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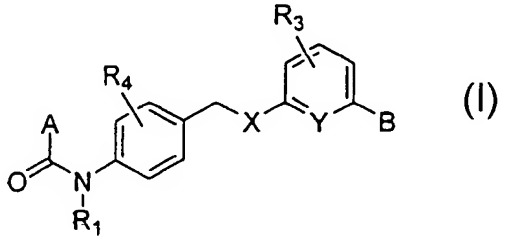
(54) Title: INHIBITORS OF INTERLEUKIN 5 GENE EXPRESSION

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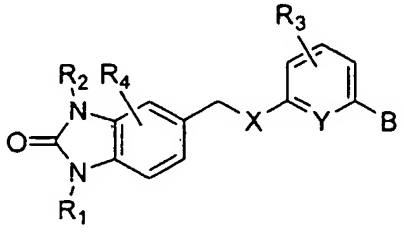


(II)

(57) Abstract: A method of inhibiting interleukin 5 gene expression in a mammal comprising administering to a mammal in need of

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# INHIBITORS OF INTERLEUKIN 5 GENE EXPRESSION

## TECHNICAL FIELD

The present invention relates to novel organic compounds that inhibit interleukin 5 (IL-5) gene expression in mammals, to pharmaceutical compositions comprising these compounds, and to a method of treating asthma.

## BACKGROUND OF INVENTION

Asthma is a chronic inflammatory disease characterized by substantial inflammation of the airways. Although inflammatory responses in general are protective mechanisms for the host, excessive or inappropriate inflammatory responses occur in certain diseases such as asthma. Common allergens such as pollen, molds, cockroaches, animal dander, and dust-mite feces contain potent antigens that can give rise to allergic responses and inflammation characteristic of asthma. The Expert Panel Report issued in 1997 by the National Asthma Education and Prevention Program and the NIH emphasizes the critical role that inflammation plays in asthma (S. Murphy, et al., Expert Panel Report 2. NIH Publication No. 97-4051 (1997)). There is evidence that early intervention with anti-inflammatory therapy modifies the disease process and that persistent asthma is most effectively controlled with daily anti-inflammatory medications (S. Murphy, et al., Expert Panel Report 2. NIH Publication No. 97-4051 (1997)).

The recognition that asthma is an inflammatory disease has led to more aggressive use of inhaled steroids and other anti-inflammatory agents. However, currently available anti-inflammatory agents are not ideal, since most have significant side-effects and/or are not amenable to oral administration. The key unmet medical needs in the treatment of asthma include the development of more specific, safer, orally active anti-inflammatory agents. Agents targeted specifically to critical events in the pathogenesis of asthma are expected to be efficacious and to have fewer side effects than most current agents.

Eosinophils and mast cells infiltrating the asthmatic airways play critical roles in the airway inflammation that occurs in asthma (G. Vogel, Science 276, 1643-1646 (1997)). In

the 1980's, attention was focused on mast cells, since these cells release a variety of inflammatory mediators upon activation by antigen. However, more recent information indicates that eosinophils also play a major role in the bronchial hyperreactivity and inflammation that are characteristic of asthma. Infiltration and activation of eosinophils in the bronchial mucosa is considered to be a central event in the pathogenesis of asthma (A.J. Wardlaw, R. Moqbel, A.B. Kay, Adv. Immunol. 60, 151-266 (1995)). The activation of both eosinophils and mast cells is orchestrated by T lymphocytes, in particular by a subset of T helper cells designated Th2 cells (A.K., Abbas, K.M., Murphy, A. Sher, Nature 383, 787-793 (1996)). T lymphocytes are central regulators of the immune system and the integrated inflammatory response to antigens. When activated by antigen, Th2 cells synthesize specific cytokines, including interleukins 4 and 5 (IL-4 and IL-5). Interleukin 4 is required both for differentiation and expansion of Th2 cells, as well as for synthesis of IgE by B lymphocytes. IgE binds to receptors on mast cells and, following binding of antigen to the IgE, the mast cells release inflammatory mediators. Interleukin 5 is a critical cytokine that regulates both the differentiation and activation of eosinophils (C. J. Sanderson, Blood 79, 3101-3109 (1992); C.J. Bagley, A.F., Lopez, M.A. Vadas, J. Allergy Clin. Immunol. 99, 725-728 (1997)).

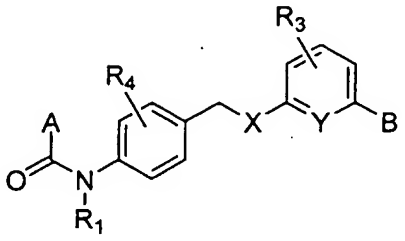
Selective inhibitors of IL-5 are expected to have highly specific effects in allergic diseases such as asthma, with few mechanism based side effects. In humans, only eosinophils and basophils are known to be affected by IL-5. The role for eosinophils in allergic late-phase bronchoconstriction is well established. Recently, basophils have also been found to participate in the pathogenesis of allergic late-phase reactions. Asthmatic patients have elevated numbers of activated T cells expressing IL-5 mRNA, which further increase following allergen challenge (D. Robinson et al. J. Allergy Clin. Immunol 92, 313-324 (1993)). The levels of IL-5 and IL-5-producing T cells in bronchial lavage of human asthmatics correlate with eosinophil infiltration, degranulation, and lung injury. Studies in experimental animals have demonstrated that IL-5 is required for generation of the eosinophilia and bronchial hyperreactivity that are characteristic of asthma. In an experimental asthma model, mice in which the IL-5 gene was ablated had significantly

reduced numbers of eosinophils as well as significantly less severe airway hyperreactivity and lung damage than the IL-5 gene-containing litter mates (P.S. Foster, J. Exp. Med. 183, 195-201 (1996)). Moreover, administration of anti-IL-5 antibodies to a variety of experimental animals decreased the airway hyperreactivity that occurred following antigen challenge of sensitized animals (R.W. Egan, In: Therapeutic Modulation of Cytokines. CRC Press (1996)).

There are no known potent, selective, nontoxic, small molecule, inhibitors of IL-5 expression or action. Broad spectrum immunosuppressants, such as cyclosporin A, as well as glucocorticoids inhibit expression of multiple cytokines and exhibit unacceptable toxicities for chronic systemic use in treatment of asthma. The present invention describes the identification of compounds which are potent inhibitors of IL-5 gene expression. Such compounds may have therapeutic potential for the treatment of asthma as well as other allergic diseases such as chronic rhinitis/sinusitis.

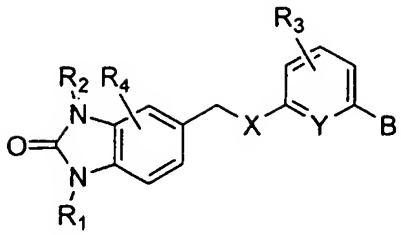
## SUMMARY OF THE INVENTION

Broadly, the present invention discloses a method of inhibiting interleukin 5 gene expression in a mammal comprising administering to a mammal in need of such treatment a pharmaceutically effective amount of one or more compounds selected from the group consisting of formula I




I,

and/or formula II,



II,

or pharmaceutically acceptable salts thereof.

In formulas I and II:

$R_1$ is selected from hydrogen and lower alkyl. Preferably, $R_1$ is methyl.

$R_2$ is selected from hydrogen and lower alkyl. Preferably, $R_2$ is methyl.

$R_3$ is selected from hydrogen, alkoxy, alkyl, cyano, halogen, haloalkoxy, haloalkyl, and $-NR_5R_6$ wherein $R_5$ and $R_6$ are each independently selected from hydrogen and alkyl. Preferably, $R_3$ is selected from hydrogen and halogen. A preferred halogen substituent is fluorine.

$R_4$ is selected from hydrogen, alkoxy, alkyl, cyano, halogen, haloalkoxy, haloalkyl, and $-NR_5R_6$ wherein $R_5$ and $R_6$ are as defined above. Preferably, $R_4$ is selected from hydrogen and halogen. A preferred halogen substituent is chlorine.

A is selected from alkenyl, alkyl, alkynyl, alkoxy, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocyclealkyl, and $NR_7R_8$ wherein $R_7$ and $R_8$ are independently selected from the group consisting of alkenyl, alkoxyalkoxyalkyl, alkoxyalkyl, alkyl, alkynyl, aryl, arylalkyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocycle, heterocyclealkyl, hydroxyalkoxyalkyl, and hydroxyalkyl. Preferably, A is selected from alkyl, alkoxy, cycloalkyl, heterocycles selected from azepanyl, azetidinyl, azocanyl, furyl, piperdinyl, pyrrolyl, pyrrolidinyl, pyrrolinyl, tetrahydropyridyl, thiazolidinyl, and thiomorpholinyl, and $NR_7R_8$ wherein $R_7$ and $R_8$ are independently selected from alkenyl, alkoxyalkyl, alkyl, alkynyl, alkoxyalkyl, alkyl, alkynyl, arylalkyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, (1,3-dioxolan-2-yl)alkyl, tetrahydro-2-furanylmethyl, hydroxyalkoxyalkyl, and hydroxyalkyl.

B is selected from heterocycle and $NR_9R_{10}$ wherein $R_9$ and $R_{10}$ are independently selected from alkenyl, alkoxyalkyl, alkyl, alkynyl, aryl, arylalkyl, cyanoalkyl, cycloalkyl,

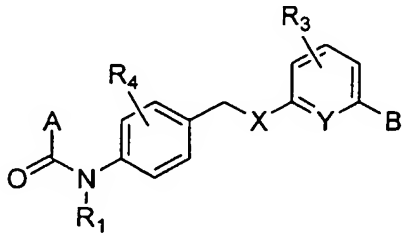
cycloalkylalkyl, haloalkyl, heterocycle, and heterocyclealkyl. Preferably, B is selected from a heterocycle selected from morpholinyl, piperazinyl, piperdinyl, pyrrolidinyl, tetrahydro-2H-pyranyl, and thiomorpholinyl, and $NR_9R_{10}$ wherein $R_9$ and $R_{10}$ are independently selected from alkoxyalkyl, alkyl, and cycloalkyl.

X is selected from $CH_2$, and O.

Y is selected from CH and N.

## DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the present invention discloses a method of inhibiting interleukin 5 gene expression in a mammal comprising administering to a mammal in need of such treatment a pharmaceutically effective amount of one or more compounds selected from formula I



I,

or a pharmaceutically acceptable salt thereof wherein,

$R_1$ is methyl; $R_3$ is selected from hydrogen and fluorine; $R_4$ is selected from hydrogen and chlorine; A is selected from azepinyl, azetidinyl, azocanyl, furyl, piperdinyl, pyrrolyl, pyrrolidinyl, 2,5-dihydro1H-pyrrolyl, tetrahydropyridyl, thiazolidinyl, and thiomorpholinyl; B is selected from morpholinyl, piperazinyl, piperdinyl, pyrrolidinyl, tetrahydro-2H-pyranyl, and thiomorpholinyl; X is selected from $CH_2$ and O; and Y is selected from CH and N.

Examples of compounds of this embodiment include, but are not limited to:

ethyl 4-{3-fluoro-5-[(4-{methyl[(2-methyl-1-pyrrolidinyl)carbonyl]amino}benzyl)oxy]phenyl}-1-piperazinecarboxylate,

N-(4-{[3-(2,6-dimethyl-4-morpholinyl)-5-fluorophenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-thiomorpholinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-hydroxy-1-piperidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-(4-acetyl-1-piperazinyl)-5-fluorophenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(1-piperidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-[4-({3-fluoro-5-[4-(2-hydroxyethyl)-1-piperazinyl]phenoxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methyl-1-piperidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(1-pyrrolidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-5-fluorophenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-hydroxy-4-phenyl-1-piperidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(3-hydroxy-1-pyrrolidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-[4-({3-fluoro-5-[4-(2-methoxyethyl)-1-piperazinyl]phenoxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1-azocanecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-3-hydroxy-N-methyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2,5-trimethyl-1-pyrrolidinecarboxamide,

(3R)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-3-hydroxy-N-methyl-1-pyrrolidinecarboxamide,

3-ethyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2,4-trimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2,5-trimethyl-2,5-dihydro-1H-pyrrole-1-carboxamide,

N-(4-{2-[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenyl]ethyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1H-pyrrole-1-carboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-2,5-dihydro-1H-pyrrole-1-carboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-3-(hydroxymethyl)-N-methyl-1-piperidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1,3-thiazolidine-3-carboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-4-(hydroxymethyl)-N-methyl-1-piperidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-3-hydroxy-N-methyl-1-piperidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-4-hydroxy-N-methyl-1-piperidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-4-thiomorpholinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-piperidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1-piperidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-3,6-dihydro-1(2H)-pyridinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1-azepanecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-4-(2-hydroxyethyl)-N-methyl-1-piperidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1-azetidinecarboxamide,

(2R)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-2-(hydroxymethyl)-N-methyl-1-pyrrolidinecarboxamide,

(2S)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-2-(hydroxymethyl)-N-methyl-1-pyrrolidinecarboxamide,

$N^1$-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-$N^1$-methyl-1,3-piperidinedicarboxamide,

N-(4-{[3-fluoro-5-(4-hydroxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-{4-[(3-fluoro-5-tetrahydro-2H-pyran-4-ylphenoxy)methyl]phenyl}-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-morpholinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

(-) N-(4-{[3-fluoro-5-(4-morpholinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

(+) N-(4-{[3-fluoro-5-(4-morpholinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(2-methyl-3-oxo-1-piperazinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

(+) N-[4-({[6-(4-hydroxytetrahydro-2H-pyran-4-yl)-2-pyridinyl]oxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide,

(-) N-[4-({[6-(4-hydroxytetrahydro-2H-pyran-4-yl)-2-pyridinyl]oxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide, and

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-2-furamide.

In another embodiment, the present invention discloses a method of inhibiting interleukin 5 gene expression in a mammal comprising administering to a mammal in need of such treatment a pharmaceutically effective amount of a compound selected from formula I or pharmaceutically acceptable salts thereof wherein, $R_1$ is methyl; $R_3$ is selected from hydrogen and fluorine; $R_4$ is selected from hydrogen and chlorine; A is $NR_7R_8$ wherein $R_7$ and $R_8$ are indpendently selected from hydrogen, alkenyl, alkoxyalkyl, alkyl, alkynyl, arylalkyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, (1,3-dioxolan-2-yl)alkyl, tetrahydro-2-furanylalkyl, hydroxyalkoxyalkyl, and hydroxyalkyl; B is selected from cyclohexyl, morpholinyl, piperazinyl, piperdinyl, tetrahydro-2H-pyranyl, pyrrolidinyl, and thiomorpholinyl; X is selected from $CH_2$ and O; and Y is selected from CH and N.

Examples of compounds of this embodiment include, but are not limited to:

ethyl 4-[3-({4-[[(diethylamino)carbonyl](methyl)amino]benzyl}oxy)-5-fluorophenyl]-1-piperazinecarboxylate,

N-(4-{[3-(2,6-dimethyl-4-morpholinyl)-5-fluorophenoxy]methyl}phenyl)-N',N'-diethyl-N-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(4-thiomorpholinyl)phenoxy]methyl}phenyl)-N'-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(4-hydroxy-1-piperidinyl)phenoxy]methyl}phenyl)-N'-methylurea,

N-(4-{[3-(4-acetyl-1-piperazinyl)-5-fluorophenoxy]methyl}phenyl)-N',N'-diethyl-N-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(1-piperidinyl)phenoxy]methyl}phenyl)-N'-methylurea,

N,N-diethyl-N'-[4-({3-fluoro-5-[4-(2-hydroxyethyl)-1-piperazinyl]phenoxy}methyl)phenyl]-N'-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(4-methyl-1-piperidinyl)phenoxy]methyl}phenyl)-N'-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(1-pyrrolidinyl)phenoxy]methyl}phenyl)-N'-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(2-methyl-3-oxo-1-piperazinyl)phenoxy]methyl}phenyl)-N'-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N',N'-trimethylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethyl-N'-propylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethylurea,

N-allyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-hydroxyethyl)-N,N'-dimethylurea,

N-(3-chloro-4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N',N'-trimethylurea,

N-(cyclopropylmethyl)-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methyl-N-propylurea,

N-ethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-isopropyl-N'-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethyl-N'-(2-propynyl)urea,

N-(2-cyanoethyl)-N-cyclopropyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea,

N-allyl-N-ethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-methoxyethyl)-N,N'-dimethylurea,

N-ethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-(2-hydroxyethyl)-N'-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-isopentyl-N,N'-dimethylurea,

N-[2-(1,3-dioxolan-2-yl)ethyl]-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethylurea,

N-ethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethylurea,

N,N-diallyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N',N'-dipropylurea,

N-butyl-N-ethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea,

N-ethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methyl-N-propylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-isopropyl-N,N'-dimethylurea,

N'-cyclobutyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-(tetrahydro-2-furanylmethyl)urea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-methoxyethyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-propylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-hydroxy-1-methylethyl)-N-methylurea,

N'-(1-ethylpropyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-(2,2,2-trifluoroethyl)urea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-neopentylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-isobutyl-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-(2-methylbutyl)urea,

N'-(2-ethylhexyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-(2-propynyl)urea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-hydroxybutyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(3-hydroxy-2,2-dimethylpropyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-[2-(2-hydroxyethoxy)ethyl]-N-methylurea,

N'-allyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-methoxy-1-methylethyl)-N-methylurea,

N'-(cyanomethyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N'-cyclopropyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-isopropyl-N-methyl-N'-propylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-[(1R)-1-(hydroxymethyl)propyl]-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-(2-methyl-2-propenyl)urea,

N'-(2-fluoroethyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N'-ethyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-hydroxypropyl)-N-methylurea,

N'-(cyclopropylmethyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N'-(2-ethylbutyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N'-cyclopentyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N'-(1,2-dimethylpropyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N'-sec-butyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N'-[bicyclo[2.2.1]hept-2-yl]-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-[2-(4-hydroxyphenyl)ethyl]-N-methylurea,

N'-(2-cyanoethyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-hydroxyethyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-[1-(hydroxymethyl)cyclopentyl]-N-methylurea,

N'-(2,2-dimethylcyclopentyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-isopropyl-N-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea,

N-ethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-(2-methoxyethyl)-N'-methylurea,

N-butyl-N-(cyanomethyl)-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea,

N-butyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-isopropyl-N'-(2-methoxyethyl)-N-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(4-hydroxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea,

N-(4-{[3-fluoro-5-(4-hydroxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N',N'-trimethylurea,

N-[4-({3-fluoro-5-[4-(2-propynyloxy)tetrahydro-2H-pyran-4-yl]phenoxy}methyl)phenyl]-N,N',N'-trimethylurea,

N,N-diethyl-N'-(4-{[3-(4-ethyltetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea,

ethyl 4-[3-({4-[[(diethylamino)carbonyl](methyl)amino]benzyl}oxy)phenyl]tetrahydro-2H-pyran-4-carboxylate,

N,N-diethyl-N'-(4-{[3-fluoro-5-(1-hydroxycyclohexyl)phenoxy]methyl}phenyl)-N'-methylurea,

N,N-diethyl-N'-{4-[(3-fluoro-5-tetrahydro-2H-pyran-4-ylphenoxy)methyl]phenyl}-N'-methylurea,

tert-butyl 4-[3-({4-[[(diethylamino)carbonyl](methyl)amino]benzyl}oxy)-5-fluorophenyl]-4-hydroxy-1-piperidinecarboxylate,

N-allyl-N'-(4-{[3-(trans-1,4-dimethoxycyclohexyl)-5-fluorophenoxy]methyl}phenyl)-N,N'-dimethylurea,

N-(4-{[3-(trans-1,4-dimethoxycyclohexyl)-5-fluorophenoxy]methyl}phenyl)-N',N'-diethyl-N-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(4-morpholinyl)phenoxy]methyl}phenyl)-N'-methylurea, and

N,N-diethyl-N'-[4-({[6-(4-hydroxytetrahydro-2H-pyran-4-yl)-2-pyridinyl]oxy}methyl)phenyl]-N'-methylurea.

In another embodiment, the present invention discloses a method of inhibiting interleukin 5 gene expression in a mammal comprising administering to a mammal in need of such treatment a pharmaceutically effective amount of a compound selected from formula I or pharmaceutically acceptable salts thereof wherein, $R_1$ is methyl; $R_3$ is selected from hydrogen and fluorine; $R_4$ is selected from hydrogen and chlorine; A is pyrrolidinyl; B is $NR_9R_{10}$ wherein $R_9$ and $R_{10}$ are independently selected from hydrogen, alkoxyalkyl, and alkyl; X is selected from $CH_2$ and O; and Y is selected from CH and N.

Examples of compounds of this embodiment include, but are not limited to:

N-[4-({3-[bis(2-methoxyethyl)amino]-5-fluorophenoxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide and

N-[4-({3-[ethyl(2-methoxyethyl)amino]-5-fluorophenoxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide.

In another embodiment, the present invention discloses a method of inhibiting interleukin 5 gene expression in a mammal comprising administering to a mammal in need of such treatment a pharmaceutically effective amount of a compound selected from formula I or a pharmaceutically acceptable salt thereof wherein, $R_1$ is methyl; $R_3$ is selected from hydrogen and fluorine; $R_4$ is selected from hydrogen and chlorine; A is $NR_7R_8$ wherein $R_7$ and $R_8$ are independently selected from hydrogen and alkyl; B is $NR_9R_{10}$ wherein $R_9$ and $R_{10}$ are independently selected from hydrogen, alkoxyalkyl, alkyl, and cycloalkyl; X is selected from $CH_2$ and O; and Y is selected from CH and N.

Examples of compounds of this embodiment include, but are not limited to:

N-[4-({3-[bis(2-methoxyethyl)amino]-5-fluorophenoxy}methyl)phenyl]-N',N'-diethyl-N-methylurea,

N-(4-{[3-(cyclopentylamino)-5-fluorophenoxy]methyl}phenyl)-N',N'-diethyl-N-methylurea,

N-(4-{[3-(cyclohexylamino)-5-fluorophenoxy]methyl}phenyl)-N',N'-diethyl-N-methylurea, and

N,N-diethyl-N'-[4-({3-[ethyl(2-methoxyethyl)amino]-5-fluorophenoxy}methyl)phenyl]-N'-methylurea.

In another embodiment, the present invention discloses a method of inhibiting interleukin 5 gene expression in a mammal comprising administering to a mammal in need of such treatment a pharmaceutically effective amount of a compound selected from formula I or a pharmaceutically acceptable salt thereof wherein, $R_1$ is methyl; $R_3$ is selected from hydrogen and fluorine; $R_4$ is selected from hydrogen and chlorine; A is selected from alkoxy, alkyl, and cycloalkyl; B is tetrahydro-2H-pyranyl; X is selected from $CH_2$ and O; and Y is selected from CH and N.

Examples of compounds of this embodiment include, but are not limited to:

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,3,3-trimethylbutanamide,

2-ethyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylbutanamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2,2-trimethylpropanamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylcyclopentanecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylcyclopropanecarboxamide,

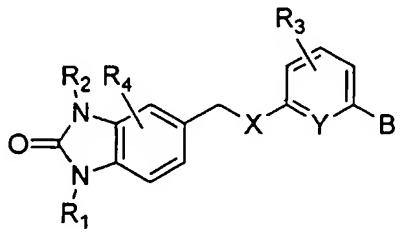
N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2-dimethylpropanamide,

isopropyl 4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl(methyl)carbamate,

propyl 4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl(methyl)carbamate, and

tert-butyl 4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl(methyl)carbamate.

In another embodiment, the present invention discloses a method of inhibiting interleukin 5 gene expression in a mammal comprising administering to a mammal in need of such treatment a pharmaceutically effective amount of a compound selected from formula II




II,

or pharmaceutically acceptable salts thereof wherein, $R_1$ is methyl; $R_2$ is methyl; $R_3$ is selected from hydrogen and fluorine; $R_4$ is selected from hydrogen and chlorine; B is selected

from cyclohexyl, piperdinyl, and tetrahydro-2H-pyranyl; X is selected from $CH_2$ and O; and Y is selected from CH and N.

Examples of compounds of this embodiment include, but are not limited to:

5-{[3-(1-benzyl-4-hydroxy-4-piperidinyl)-5-fluorophenoxy]methyl}-1,3-dimethyl-1,3-dihydro-2H-benzimidazol-2-one,

5-{[3-(trans-1,4-dimethoxycyclohexyl)-5-fluorophenoxy]methyl}-1,3-dimethyl-1,3-dihydro-2H-benzimidazol-2-one,

5-{[3-fluoro-5-(8-hydroxy-1,4-dioxaspiro[4.5]dec-8-yl)phenoxy]methyl}-1,3-dimethyl-1,3-dihydro-2H-benzimidazol-2-one, and

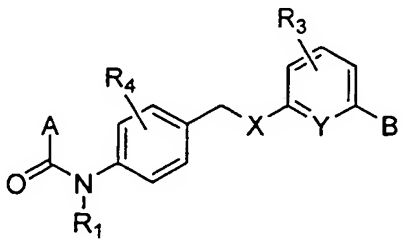
5-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}-1,3-dimethyl-1,3-dihydro-2H-benzimidazol-2-one.

Another embodiment of the present invention relates to pharmaceutical compositions comprising a therapeutically effective amount of a compound of formula I-II or a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier.

Another embodiment of the present invention relates to a method of treating allergic diseases comprising administering a therapeutically effective amount of a compound of formula I-II or a pharmaceutically acceptable salt thereof.

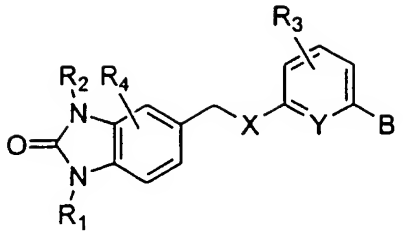
Another embodiment of the present invention relates to a method of treating asthma comprising administering a therapeutically effective amount of a compound of formula I-II or a pharmaceutically acceptable salt thereof.

In another embodiment of the present invention are disclosed compounds of formula I




I

and of formula II



II,

or pharmaceutically acceptable salts thereof wherein, in formulas I and II:

$R_1$ is selected from hydrogen and lower alkyl;

$R_2$ is selected from hydrogen and lower alkyl;

$R_3$ is selected from hydrogen, alkoxy, alkyl, cyano, halogen, haloalkoxy, haloalkyl, and $-NR_5R_6$ wherein $R_5$ and $R_6$ are independently selected from hydrogen and alkyl;

$R_4$ is selected from hydrogen, alkoxy, alkyl, cyano, halogen, haloalkoxy, haloalkyl, and $-NR_5R_6$ wherein $R_5$ and $R_6$ are independently selected from hydrogen and alkyl;

A is selected from the group consisting of alkenyl, alkyl, alkynyl, alkoxy, aryl, arylalkyl, cycloalkyl,cycloalkylalkyl, heterocycle, heterocyclealkyl, and $NR_7R_8$ wherein $R_7$ and $R_8$ are independently selected from alkenyl, alkoxyalkoxyalkyl, alkoxyalkyl, alkyl, alkynyl, aryl, arylalkyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocycle, heterocyclealkyl, hydroxyalkoxyalkyl, and hydroxyalkyl;

B is selected from the group consisting of heterocycle and $NR_9R_{10}$ wherein $R_9$ and $R_{10}$ are independently selected from alkenyl, alkoxyalkyl, alkyl, alkynyl, aryl, arylalkyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocycle, and heterocyclealkyl;

X is selected from $CH_2$ and O; and

Y is selected from CH and N;

provided that for compounds of formula I when $R_4$ is hydrogen and A is piperdinyl, morpholinyl, thiomorpholinyl, piperazinyl, or $NR_7R_8$ and $R_7$ and $R_8$ are independently selected from the group consisting of hydrogen, alkyl, haloalkyl, and hydroxyalkyl then B is other than tetrahydro-2H-pyran-4-yl optionally substituted with 1 subsituent selected from the group consisting of hydroxy and alkoxy or cyclohexyl optionally substituted with 1 subsituent selected from the group consisting of hydroxy and alkoxy; and

further provided that for compounds of formula II when $R_3$ is hydrogen and $R_4$ is hydrogen then B is other than cyclohexyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkyl and hydroxy.

In another embodiment of the present invention are disclosed compounds of formula I wherein, $R_1$ is methyl; $R_3$ is selected from hydrogen and fluorine; $R_4$ is selected from hydrogen and chlorine; A is selected from azetidinyl, azepanyl, azocanyl, furyl, pyrrolyl, pyrrolidinyl, pyrrolinyl, thiazolidinyl, and tetrahydropyridyl; B is selected from the group consisting of morpholinyl, piperazinyl, piperdinyl, tetrahydro-2H-pyranyl, pyrrolidinyl, thiomorpholinyl, and $NR_9R_{10}$ wherein $R_9$ and $R_{10}$ are independently selected from alkoxyalkyl and alkyl; X is selected from $CH_2$ and O; and Y is CH.

Examples of compounds of this embodiment include, but are not limited to:

ethyl 4-{3-fluoro-5-[(4-{methyl[(2-methyl-1-pyrrolidinyl)carbonyl]amino}benzyl)oxy]phenyl}-1-piperazinecarboxylate,

N-[4-({3-[bis(2-methoxyethyl)amino]-5-fluorophenoxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-(2,6-dimethyl-4-morpholinyl)-5-fluorophenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-thiomorpholinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-hydroxy-1-piperidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-(4-acetyl-1-piperazinyl)-5-fluorophenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(1-piperidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-[4-({3-fluoro-5-[4-(2-hydroxyethyl)-1-piperazinyl]phenoxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methyl-1-piperidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-[4-({3-[ethyl(2-methoxyethyl)amino]-5-fluorophenoxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(1-pyrrolidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-5-fluorophenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-hydroxy-4-phenyl-1-piperidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(3-hydroxy-1-pyrrolidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-[4-({3-fluoro-5-[4-(2-methoxyethyl)-1-piperazinyl]phenoxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1-azocanecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-3-hydroxy-N-methyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2,5-trimethyl-1-pyrrolidinecarboxamide,

(3R)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-3-hydroxy-N-methyl-1-pyrrolidinecarboxamide,

3-ethyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2,4-trimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2,5-trimethyl-2,5-dihydro-1H-pyrrole-1-carboxamide,

N-(4-{2-[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenyl]ethyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1H-pyrrole-1-carboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-2,5-dihydro-1H-pyrrole-1-carboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1,3-thiazolidine-3-carboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-3,6-dihydro-1(2H)-pyridinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1-azepanecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1-azetidinecarboxamide,

(2R)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-2-(hydroxymethyl)-N-methyl-1-pyrrolidinecarboxamide,

(2S)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-2-(hydroxymethyl)-N-methyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-hydroxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-{4-[(3-fluoro-5-tetrahydro-2H-pyran-4-ylphenoxy)methyl]phenyl}-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-morpholinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

(-) N-(4-{[3-fluoro-5-(4-morpholinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

(+) N-(4-{[3-fluoro-5-(4-morpholinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(2-methyl-3-oxo-1-piperazinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide, and

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-2-furamide.

In another embodiment of the present invention are disclosed compounds of formula I wherein, $R_1$ is methyl; $R_3$ is selected from hydrogen and fluorine; $R_4$ is selected from hydrogen and chlorine; A is $NR_7R_8$ wherein $R_7$ and $R_8$ are independently selected from hydrogen, alkenyl, alkoxyalkyl, alkyl, alkynyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, (1,3-dioxolan-2-yl)alkyl, tetrahydro-2-furanylalkyl, hydroxyalkoxyalkyl, and phenylalkyl; B is selected from tetrahydro-2H-pyranyl and cyclohexyl; X is selected from $CH_2$ and O; and Y is CH.

Examples of compounds of this embodiment include, but are not limited to:

N-allyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethylurea,

N-(3-chloro-4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N',N'-trimethylurea,

N-(cyclopropylmethyl)-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methyl-N-propylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethyl-N'-(2-propynyl)urea,

N-(2-cyanoethyl)-N-cyclopropyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea,

N-allyl-N-ethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-methoxyethyl)-N,N'-dimethylurea,

N-[2-(1,3-dioxolan-2-yl)ethyl]-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethylurea,

N,N-diallyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea,

N'-cyclobutyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-(tetrahydro-2-furanylmethyl)urea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-methoxyethyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-(2-propynyl)urea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-[2-(2-hydroxyethoxy)ethyl]-N-methylurea,

N'-allyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-methoxy-1-methylethyl)-N-methylurea,

N'-(cyanomethyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N'-cyclopropyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-(2-methyl-2-propenyl)urea,

N'-(cyclopropylmethyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N'-cyclopentyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N'-[bicyclo[2.2.1]hept-2-yl]-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-[2-(4-hydroxyphenyl)ethyl]-N-methylurea,

N'-(2-cyanoethyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-[1-(hydroxymethyl)cyclopentyl]-N-methylurea,

N'-(2,2-dimethylcyclopentyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-ethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-(2-methoxyethyl)-N'-methylurea,

N-butyl-N-(cyanomethyl)-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea,

N-[4-({3-fluoro-5-[4-(2-propynyloxy)tetrahydro-2H-pyran-4-yl]phenoxy}methyl)phenyl]-N,N',N'-trimethylurea,

N,N-diethyl-N'-(4-{[3-(4-ethyltetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea,

ethyl 4-[3-({4-[[(diethylamino)carbonyl](methyl)amino]benzyl}oxy)phenyl]tetrahydro-2H-pyran-4-carboxylate, and

N,N-diethyl-N'-{4-[(3-fluoro-5-tetrahydro-2H-pyran-4-ylphenoxy)methyl]phenyl}-N'-methylurea.

In another embodiment of the present invention are disclosed compounds of formula I wherein, $R_1$ is methyl; $R_3$ is selected from hydrogen and fluorine; $R_4$ is selected from hydrogen and chlorine; A is $NR_7R_8$ wherein $R_4$ and $R_5$ are independently selected from hydrogen and alkyl; B is selected from morpholinyl, piperazinyl, piperdinyl, pyrrolidinyl, thiomorpholinyl, and $NR_9R_{10}$ wherein $R_9$ and $R_{10}$ are independently selected from the group consisting of hydrogen, alkoxyalkyl, alkyl, and cycloalkyl; X is selected from $CH_2$ and O; and Y is CH.

Examples of compounds of this embodiment include, but are not limited to:

ethyl 4-[3-({4-[[(diethylamino)carbonyl](methyl)amino]benzyl}oxy)-5-fluorophenyl]-1-piperazinecarboxylate,

N-[4-({3-[bis(2-methoxyethyl)amino]-5-fluorophenoxy}methyl)phenyl]-N',N'-diethyl-N-methylurea,

N-(4-{[3-(2,6-dimethyl-4-morpholinyl)-5-fluorophenoxy]methyl}phenyl)-N',N'-diethyl-N-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(4-thiomorpholinyl)phenoxy]methyl}phenyl)-N'-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(4-hydroxy-1-piperidinyl)phenoxy]methyl}phenyl)-N'-methylurea,

N-(4-{[3-(4-acetyl-1-piperazinyl)-5-fluorophenoxy]methyl}phenyl)-N',N'-diethyl-N-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(1-piperidinyl)phenoxy]methyl}phenyl)-N'-methylurea,

N-(4-{[3-(cyclopentylamino)-5-fluorophenoxy]methyl}phenyl)-N',N'-diethyl-N-methylurea,

N-(4-{[3-(cyclohexylamino)-5-fluorophenoxy]methyl}phenyl)-N',N'-diethyl-N-methylurea,

N,N-diethyl-N'-[4-({3-fluoro-5-[4-(2-hydroxyethyl)-1-piperazinyl]phenoxy}methyl)phenyl]-N'-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(4-methyl-1-piperidinyl)phenoxy]methyl}phenyl)-N'-methylurea,

N,N-diethyl-N'-[4-({3-[ethyl(2-methoxyethyl)amino]-5-fluorophenoxy}methyl)phenyl]-N'-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(1-pyrrolidinyl)phenoxy]methyl}phenyl)-N'-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(2-methyl-3-oxo-1-piperazinyl)phenoxy]methyl}phenyl)-N'-methylurea,

tert-butyl 4-[3-({4-[[(diethylamino)carbonyl](methyl)amino]benzyl}oxy)-5-fluorophenyl]-4-hydroxy-1-piperidinecarboxylate, and

N,N-diethyl-N'-(4-{[3-fluoro-5-(4-morpholinyl)phenoxy]methyl}phenyl)-N'-methylurea.

In another embodiment of the present invention are disclosed compounds of formula I wherein, $R_1$ is methyl; $R_3$ is selected from hydrogen and fluorine; $R_4$ is chlorine; A is $NR_7R_8$ wherein $R_7$ and $R_8$ are independently selected from the group consisting of hydrogen and alkyl; B is tetrahydro-2H-pyranyl; X is O; and
Y is CH.

An Example of compounds of this embodiment include, but are not limited to:

N-(3-chloro-4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N',N'-trimethylurea.

In another embodiment of the present invention are disclosed compounds of formula I wherein, $R_1$ is methyl; $R_3$ is hydrogen; $R_4$ is hydrogen; A is selected from the group consisting of pyrrolidinyl and $NR_7R_8$ wherein $R_7$ and $R_8$ are independently selected from hydrogen and alkyl; B is tetrahydro-2H-pyranyl; X is O; and Y is N.

Examples of compounds of this embodiment include, but are not limited to:

(+) N-[4-({[6-(4-hydroxytetrahydro-2H-pyran-4-yl)-2-pyridinyl]oxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide,

(-) N-[4-({[6-(4-hydroxytetrahydro-2H-pyran-4-yl)-2-pyridinyl]oxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide, and

N,N-diethyl-N'-[4-({[6-(4-hydroxytetrahydro-2H-pyran-4-yl)-2-pyridinyl]oxy}methyl)phenyl]-N'-methylurea.

In another embodiment of the present invention are disclosed compounds of formula I wherein, $R_1$ is methyl; $R_3$ is selected from hydrogen and halogen; $R_4$ is selected from hydrogen and halogen; A is selected from the group consisting of alkoxy, alkyl, and cycloalkyl; B is tetrahydro-2H-pyranyl; X is O; and Y is CH.

Examples of compounds of this embodiment include, but are not limited to:

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,3,3-trimethylbutanamide,

2-ethyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylbutanamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2,2-trimethylpropanamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylcyclopentanecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylcyclopropanecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2-dimethylpropanamide,

isopropyl 4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl(methyl)carbamate,

propyl 4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl(methyl)carbamate, and

tert-butyl 4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl(methyl)carbamate.

In another embodiment of the present invention are disclosed compounds of formula II wherein, $R_1$ is methyl; $R_2$ is methyl; $R_3$ is halogen; $R_4$ is selected from hydrogen and halogen; B is selected from cyclohexyl, piperdinyl, and tetrahydro-2H-pyranyl; X is O; and Y is CH.

Examples of compounds of this embodiment include, but are not limited to:

5-{[3-(1-benzyl-4-hydroxy-4-piperidinyl)-5-fluorophenoxy]methyl}-1,3-dimethyl-1,3-dihydro-2H-benzimidazol-2-one,

5-{[3-(trans-1,4-dimethoxycyclohexyl)-5-fluorophenoxy]methyl}-1,3-dimethyl-1,3-dihydro-2H-benzimidazol-2-one,

5-{[3-fluoro-5-(8-hydroxy-1,4-dioxaspiro[4.5]dec-8-yl)phenoxy]methyl}-1,3-dimethyl-1,3-dihydro-2H-benzimidazol-2-one, and

5-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}-1,3-dimethyl-1,3-dihydro-2H-benzimidazol-2-one.

Definition of Terms

As used throughout this specification and the appended claims, the following terms have the following meanings.

The term "alkenyl," as used herein, refers to a straight or branched chain hydrocarbon containing from 2 to 10 carbons and containing at least one carbon-carbon double bond formed by the removal of two hydrogens. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, 3-decenyl and the like.

The term "alkenyloxy," as used herein, refers to an alkenyl group, as defined herein, appended to the parent molecular moiety through an oxy moiety, as defined herein. Representative examples of alkenyloxy include, but are not limited to, 2-propenyloxy (allyloxy), 2-butenyloxy, 3-butenyloxy, and the like.

The term "alkoxy," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through an oxy moiety, as defined herein. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy and the like.

The term "alkoxyalkoxy," as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through another alkoxy group, as defined herein. Representative examples of alkoxyalkoxy include, but are not limited to, tert-butoxymethoxy, 2-ethoxyethoxy, 2-methoxyethoxy, methoxymethoxy, and the like.

The term "alkoxyalkoxyalkyl," as used herein, refers to an alkoxyalkoxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkoxyalkoxyalkyl include, but are not limited to, tert-butoxymethoxymethyl, ethoxymethoxymethyl, (2-methoxyethoxy)methyl, 2-(2-methoxyethoxy)ethyl, and the like.

The term "alkoxyalkyl," as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein.

Representative examples of alkoxyalkyl include, but are not limited to, tert-butoxymethyl, 2-ethoxyethyl, 2-methoxyethyl, methoxymethyl, and the like.

The term "alkoxycarbonyl," as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkoxycarbonyl include, but are not limited to, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, and the like.

The term "alkyl," as used herein, refers to a straight or branched chain hydrocarbon containing from 1 to 10 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, 2-ethylhexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, and the like.

The term "alkylcarbonyl," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkylcarbonyl include, but are not limited to, acetyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, and the like.

The term "alkylcarbonyloxy," as used herein, refers to an alkylcarbonyl group, as defined herein, appended to the parent molecular moiety through an oxy moiety, as defined herein. Representative examples of alkylcarbonyloxy include, but are not limited to, acetyloxy, ethylcarbonyloxy, tert-butylcarbonyloxy, and the like.

The term "alkylene," denotes a divalent group derived from a straight or branched chain hydrocarbon of from 1 to 10 carbon atoms. Representative examples of alkylene include, but are not limited to, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, and the like.

The term "alkylthio," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a thio moiety, as defined herein. Representative examples of alkylthio include, but are not limited, methylsulfanyl, ethylsulfanyl, tert-butylsulfanyl, hexylsulfanyl, and the like.

The term "alkynyl," as used herein, refers to a straight or branched chain hydrocarbon group containing from 2 to 10 carbon atoms and containing at least one carbon-carbon triple

bond. Representative examples of alkynyl include, but are not limited, to acetylenyl, 1-propynyl, 2-propynyl, 3-butynyl, 2-pentynyl, 1-butynyl and the like.

The term "alkynyloxy," as used herein, refers to an alkynyl group, as defined herein, appended to the parent molecular moiety through an oxy moiety, as defined herein. Representative examples of alkynyloxy include, but are not limited to, 2-propynyloxy, 2-butynyloxy, 3-butynyloxy, and the like.

The term "aryl," as used herein, refers to a monocyclic-ring system, or a bicyclic-fused ring system wherein one or both of the fused rings are aromatic. Representative examples of aryl include, but are not limited to, azulenyl, indanyl, indenyl, naphthyl, phenyl, dihydronaphthyl, tetrahydronaphthyl, and the like.

The aryl groups of this invention can be substituted with 1, 2, or 3 substituents independently selected from alkenyl, alkenyloxy, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkylthio, alkynyl, alkynyloxy, aryl, arylalkoxyalkyl, arylalkoxycarbonyl, arylalkyl, carboxy, cyano, ethylenedioxy, formyl, halo, haloalkyl, heterocycle, hydroxy, hydroxyalkyl, mercapto, nitro, $-NR_{90}R_{91}$, and $(NR_{92}R_{93})$carbonyl.

The term "arylalkoxy," as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein. Representative examples of arylalkoxy include, but are not limited to, benzyloxy, 2-phenylethoxy, 3-naphth-2-ylpropoxy, 5-phenylpentyloxy, and the like.

The term "arylalkoxyalkyl," as used herein, refers to an arylalkoxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of arylalkoxyalkyl include, but are not limited to, benzyloxymethyl, 2-phenylethoxymethyl, 3-naphth-2-ylpropoxymethyl, 5-phenylpentyloxymethyl, and the like.

The term "arylalkoxycarbonyl," as used herein, refers to an arylalkoxy group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of arylalkoxycarbonyl include, but are not limited to, benzyloxycarbonyl, naphth-2-ylmethoxycarbonyl, and the like.

The term "arylalkyl," as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of arylalkyl include, but are not limited to, benzyl, 2-phenylethyl, 2-(4-hydroxyphenyl)ethyl, 3-phenylpropyl, 2-naphth-2-ylethyl, and the like.

The term "arylcarbonyl," as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of arylcarbonyl include, but are not limited to, benzoyl, naphthoyl, and the like.

The term "carbonyl," as used herein, refers to a -C(O)- group.

The term "carboxy," as used herein, refers to a $-CO_2H$ group.

The term "carboxyalkyl," as used herein, refers to a carboxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of carboxyalkyl include, but are not limited to, carboxymethyl, 2-carboxyethyl, 3-carboxypropyl, and the like.

The term "cyano," as used herein, refers to a -CN group.

The term "cyanoalkyl," as used herein, refers to a cyano group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of cyanoalkyl include, but are not limited to, cyanomethyl, 2-cyanoethyl, 3-cyanopropyl, and the like.

The term "cycloalkyl," as used herein, refers to a monocyclic, bicyclic, or tricyclic ring system. Monocyclic ring systems are exemplified by a saturated cyclic hydrocarbon group containing from 3 to 8 carbon atoms. Representative examples of monocyclic ring systems include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. Bicyclic ring systems are exemplified by a bridged monocyclic ring system in which two non-adjacent carbon atoms of the monocyclic ring are linked by an alkylene bridge of between one and three additional carbon atoms. Representative examples of bicyclic ring systems include, but are not limited to, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.1]nonane, bicyclo[4.2.1]nonane, and the like. Tricyclic ring systems are

exemplified by a bicyclic ring system in which two non-adjacent carbon atoms of the bicyclic ring are linked by a bond or an alkylene bridge of between one and three carbon atoms. Representative examples of tricyclic-ring systems include, but are not limited to, tricyclo[3.3.1.$0^{3,7}$]nonane, tricyclo[3.3.1.$1^{3,7}$]decane (adamantane), and the like.

The cycloalkyl groups of this invention can be substituted with 1, 2, or 3 substituents independently selected from alkenyl, alkenyloxy, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkylthio, alkynyl, alkynyloxy, aryl, arylalkoxycarbonyl, carboxy, cyano, ethylenedioxy, formyl, halo, haloalkyl, heterocycle, hydroxy, hydroxyalkyl, mercapto, oxo, -$NR_{90}R_{91}$, and ($NR_{92}R_{93}$)carbonyl.

The term "cycloalkylalkyl," as used herein, refers to cycloalkyl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of cycloalkylalkyl include, but are not limited to, cyclopropylmethyl, 2-cyclobutylethyl, cyclopentylmethyl, cyclohexylmethyl and 4-cycloheptylbutyl, and the like.

The term "ethylenedioxy," as used herein, refers to a -$O(CH_2)_2O$- group wherein the oxygen atoms of the ethylenedioxy group are attached to the parent molecular moiety through one carbon atom forming a 5 membered ring or the oxygen atoms of the ethylenedioxy group are attached to the parent molecular moiety through two adjacent carbon atoms forming a six membered ring.

The term "formyl," as used herein, refers to a -C(O)H group.

The term "halo" or "halogen," as used herein, refers to -Cl, -Br, -I or -F.

The term "haloalkoxy," as used herein, refers to at least one halogen, as defined herein, appended to the parent molecular moiety through an alkoxy group of one to four carbons, as defined herein. Representative examples of haloalkoxy include, but are not limited to, bromomethoxy, chloromethoxy, 2-fluoroethoxy, trifluoromethoxy, pentafluoroethoxy, 2,2,2-trifluoroethoxy, and the like.

The term "haloalkyl," as used herein, refers to at least one halogen, as defined herein, appended to the parent molecular moiety through an alkyl group of one to four carbons, as defined herein. Representative examples of haloalkyl include, but are not limited to,

bromomethyl, chloromethyl, 2-fluoroethyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, and the like.

The term "heterocycle" or "heterocyclic," as used herein, refers to a monocyclic ring system. Monocyclic ring systems are exemplified by any 3 or 4 membered ring containing a heteroatom independently selected from oxygen, nitrogen and sulfur; or a 5, 6, 7, or 8 membered ring containing one, two or three heteroatoms wherein the heteroatoms are independently selected from nitrogen, oxygen and sulfur. The 5-membered ring has from 0-2 double bonds and the 6- and 7-membered ring have from 0-3 double bonds. Representative examples of monocyclic ring systems include, but are not limited to, azetidinyl, azepanyl, aziridinyl, azocanyl, diazepinyl, 2,5-dihydro-1H-pyrrolyl, 1,3-dioxolanyl, dioxanyl, dithianyl, furyl, imidazolyl, imidazolinyl, imidazolidinyl, isothiazolyl, isothiazolinyl, isothiazolidinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, morpholinyl, oxadiazolyl, oxadiazolinyl, oxadiazolidinyl, oxazolyl, oxazolinyl, oxazolidinyl, piperazinyl, piperidinyl, pyranyl, pyrazinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, pyridyl, pyrimidinyl, pyridazinyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydro-2H-pyranyl, tetrahydropyridyl, tetrahydrothienyl, tetrazinyl, tetrazolyl, thiadiazolyl, thiadiazolinyl, thiadiazolidinyl, thiazolyl, thiazolinyl, thiazolidinyl, thienyl, thiomorpholinyl, 1,1-dioxidothiomorpholinyl, thiopyranyl, triazinyl, triazolyl, and the like.

The heterocycles of this invention can be substituted with 1, 2, or 3 substituents independently selected from alkenyl, alkenyloxy, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkylthio, alkynyl, alkynyloxy, aryl, arylalkoxyalkyl, arylalkoxycarbonyl, arylalkyl, arylcarbonyl, carboxy, carboxyalkyl, cyano, cyanoalkyl, ethylenedioxy, formyl, halo, haloalkyl, heterocycle, hydroxy, hydroxyalkyl, mercapto, nitro, oxo, $-NR_{90}R_{91}$, and $(NR_{92}R_{93})$carbonyl. Representative examples of heterocycles substituted with 1, 2, or 3 substituents include, but are not limited to, 1,4-dioxa-8-azaspiro[4.5]decane, 2-methylpyrrolidinyl, 4-hydroxy-4-phenyl-1-piperdinyl, 2-hydroxymethylpyrrolidinyl, 3-hydroxypyrrolidinyl, 2-hydroxyethyl-1-piperazinyl, and the like.

The term "heterocyclealkyl," as used herein, refers to a heterocycle, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of heterocyclealkyl include, but are not limited to, pyrid-3-ylmethyl, 2-pyrimidin-2-ylpropyl, 2-(1,3-dioxolan-2-yl)ethyl, tetrahydro-2-furanylmethyl, and the like.

The term "hydroxy," as used herein, refers to an -OH group.

The term "hydroxyalkyl," as used herein, refers to a hydroxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of hydroxyalkyl include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, and the like.

The term "lower alkyl," as used herein, refers to a straight or branched chain hydrocarbon group containing from 1-to-4 carbon atoms. Representative examples of lower alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, and the like.

The term "-$NR_{90}R_{91}$," as used herein, refers to two groups, $R_{90}$ and $R_{91}$, which are appended to the parent molecular moiety through a nitrogen atom. $R_{90}$ and $R_{91}$ are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl. Representative examples of -$NR_{90}R_{91}$ include, but are not limited to, amino, benzylamino, methylamino, acetylamino, acetylmethylamino, phenylamino, and the like.

The term "-$NR_{92}R_{93}$," as used herein, refers to two groups, $R_{92}$ and $R_{93}$, which are appended to the parent molecular moiety through a nitrogen atom. $R_{92}$ and $R_{93}$ are independently selected from hydrogen, alkyl, aryl, and arylalkyl. Representative examples of -$NR_{92}R_{93}$ include, but are not limited to, amino, benzylamino, methylamino, dimethylamino, ethylamino, phenylamino, and the like.

The term "($NR_{92}R_{93}$)carbonyl," as used herein, refers to a -$NR_{92}R_{93}$ group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of ($NR_{92}R_{93}$)carbonyl include, but are not limited to, aminocarbonyl, benzylaminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, ethylaminocarbonyl, phenylaminocarbonyl, and the like.

The term "mercapto," as used herein, refers to a -SH group.

The term "nitro," as used herein, refers to a $-NO_2$ group.

The term "oxo," as used herein, refers to a =O moiety.

The term "oxy," as used herein, refers to a -O- moiety.

The term "thio," as used herein, refers to a -S- moiety.

The compounds of the present invention can be used in the form of pharmaceutically acceptable salts derived from inorganic or organic acids. The term "pharmaceutically acceptable salt," as used herein, refers to those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well-known in the art. For example, S. M. Berge et al. describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66: 1 et seq. The salts can be prepared in situ during the final isolation and purification of the compounds of the present invention or separately by reacting a free base function with a suitable organic acid. Representative acid addition salts include, but are not limited to acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsufonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isethionate), lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, phosphate, glutamate, bicarbonate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; arylalkyl halides like benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained. Examples of acids which can be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid.

Basic addition salts can be prepared in situ during the final isolation and purification of compounds of this invention by reacting a carboxylic acid-containing moiety with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on alkali metals or alkaline earth metals such as lithium, sodium, potassium, calcium, magnesium and aluminum salts and the like and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine and the like. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine and the like.

Compounds of the present invention can exist as stereoisomers, wherein asymmetric or chiral centers are present. Stereoisomers are designated "R" or "S," depending on the configuration of substituents around the chiral carbon atom. The terms "R" and "S" used herein are configurations as defined in (IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem., (1976), 45: 13-30). The present invention contemplates various stereoisomers and mixtures thereof and are specifically included within the scope of this invention. Stereoisomers include enantiomers, diastereomers, and mixtures of enantiomers or diastereomers. Individual stereoisomers of compounds of the present invention may be prepared synthetically from commercially available starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution well-known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic columns.

The present invention contemplates pharmaceutically active metabolites formed by in vivo biotransformation of compounds of formula I-II. The term pharmaceutically active metabolite, as used herein, refers to a compound formed by the in vivo biotransformation of

compounds of formula I-II. The present invention contemplates compounds of formula I-II and metabolites thereof. A thorough discussion of biotransformation is provided in (Goodman and Gilman's, The Pharmacological Basis of Therapeutics, seventh edition).

Interleukin 5 Gene Expression Inhibition Determination

Compounds of the present invention were evaluated as inhibitors of interleukin 5 gene expression in an assay involving stimulated human T lymphocytes.

Cells of the human cutaneous T cell lymphoma cell line, HUT 78 (ATCC, Rockville, MD) were cultured in RPMI 1640 medium containing 10% (v/v) fetal bovine serum, 2 mM L-glutamine and 1% penicillin/streptomycin (100 units/mL and 100 μg/mL final concentration, respectively) (Life Technologies, Gaithersburg, MD). Three days prior to stimulation, the HUT 78 cells were seeded at a density of $2 \times 10^5$ cells/mL. Three days later and immediately prior to stimulation, cells (at ~$1 \times 10^6$/mL) were centrifuged at 1200 rpm for 10 minutes at room temperature, and resuspended in fresh growth medium at a density of $1 \times 10^6$cells/mL. Cells were then pretreated with compounds of the present invention, followed by stimulation with anti-CD3 (clone X-35, Coulter-Immunotech, Miami, FL) and phorbol 12-myristate 13-acetate (PMA) (Sigma, St. Louis, MO) as follows. Two hundred microliters of the cell suspension were added to each well of a 96-well cell culture plate and pretreated for 15 minutes at room temperature with or without various concentrations of compounds of the present invention by adding 8 μL of half-log serial dilutions of a stock solution of the compound in growth medium containing 1% dimethylsulfoxide (DMSO, Sigma). Cells in each well were then transferred to a second 96-well culture plate which had been pre-coated with 150 ng/well of anti-CD3, followed by the addition of PMA to a final concentration of 2 ng/mL. Cells were subsequently incubated for 30 hours at 37 °C in the presence of 5% $CO_2$. After 30 hours, cells were harvested by centrifugation at 1200 rpm for 10 minutes at 4 °C, and the supernatants harvested for measurement of IL-5 levels secreted from the cells using an enzyme linked immunosorbent assay (ELISA).

For the IL-5 ELISA assay, 100 μL of HUT 78 cell supernatants were added to wells of an Immulon 4 HBX plate (Dynex, Chantilly, VA) that had been pre-coated with 100 μL of

a 1 μg/mL solution of rat anti-human IL-5 antibody (clone TRFK5, Pharmingen, San Diego, CA). After incubation for 2 hours at room temperature, the plate was washed and each well was subsequently incubated for 1-2 hours at room temperature with 100 μL of a 1 μg/mL solution of biotinylated rat anti-human IL-5 antibody (clone JES1-5A10, Pharmingen). The plate was then washed again, and each well was incubated with 100 μL of a 1 μg/mL solution of streptavidin-horseradish peroxidase conjugate (Pierce, Rockford, IL) for 1 hour, followed by incubation with 100 μL substrate [0.3 g/L 2,2'-azino-di-(3-ethylbenzthiazoline-6-sulfonate); ABTS] (Kirkegaard & Perry Laboratories, Gaithersburg, MD) for 15-30 minutes. After addition of 100 μL of ABTS stop solution (Kirkegaard & Perry Laboratories, Gaithersburg, MD), the plate was read at an O.D. of 405 nm. Human IL-5 used in the standard curve was from R&D Systems, Inc., Minneapolis, MN. The percent inhibition of IL-5 expression produced by each concentration of compounds of the present invention was calculated relative to IL-5 levels produced by the stimulated control cells. The $IC_{50}$ values, shown in Table 1, were graphically determined from 8-point dose response curves generated for each compound. IL-5 protein levels in the supernatant from stimulated HUT 78 cells were approximately 1500 pg/mL, whereas no IL-5 was detectable from unstimulated cells.

Table 1: $IC_{50}$ Values (nM)

| Example | $IC_{50}$ (nM) |
|---|---|
| 1 | 80 |
| 2 | 300 |
| 3 | 450 |
| 4 | 190 |
| 5 | 40 |
| 6 | 190 |
| 7 | 150 |
| 8 | 800 |
| 9 | 900 |
| 10 | 850 |

| | |
|---|---|
| 11 | 400 |
| 12 | 250 |
| 13 | 80 |
| 14 | 200 |
| 15 | 0.7 |
| 16 | 30 |
| 17 | 80 |
| 18 | 12 |
| 19 | 8 |
| 20 | 40 |
| 21 | 15 |
| 22 | 150 |
| 23 | 35 |
| 24 | 60 |
| 25 | 4 |
| 26 | 3 |
| 27 | 30 |
| 28 | 0.5 |
| 29 | 10 |
| 30 | 400 |
| 31 | 400 |
| 32 | 3 |
| 33 | 90 |
| 37 | 200 |
| 38 | 100 |
| 41 | 500 |
| 42 | 640 |
| 43 | 600 |

| | |
|---|---|
| 44 | 750 |
| 46 | 550 |
| 47 | 10 |
| 48 | 23 |
| 49 | 1000 |
| 50 | 750 |
| 51 | 70 |
| 53 | 60 |
| 54 | 900 |
| 61 | 50 |
| 65 | 220 |
| 66 | 400 |
| 68 | 250 |
| 73 | 300 |
| 74 | 40 |
| 75 | 900 |
| 76 | 600 |
| 85 | 450 |
| 88 | 450 |
| 89 | 170 |
| 90 | 120 |
| 91 | 320 |
| 92 | 30 |
| 95 | 180 |
| 96 | 270 |
| 100 | 90 |
| 102 | 890 |
| 103 | 200 |

| | |
|---|---|
| 106 | 800 |
| 107 | 300 |
| 108 | 60 |
| 110 | 250 |
| 111 | 400 |
| 114 | 500 |
| 115 | 1000 |
| 118 | 1000 |
| 120 | 16 |
| 126 | 0.05 |
| 128 | 40 |
| 129 | 350 |
| 130 | 5 |
| 131 | 300 |
| 132 | 400 |
| 133 | 320 |
| 135 | 1 |
| 136 | 0.05 |
| 137 | 400 |
| 138 | 78 |
| 139 | 70 |
| 140 | 58 |
| 141 | 46 |
| 143 | 1000 |
| 144 | 60 |
| 145 | 100 |
| 146 | 150 |
| 147 | 150 |

| | |
|---|---|
| 148 | 250 |
| 149 | 300 |
| 150 | 400 |
| 151 | 300 |
| 152 | 850 |
| 153 | 340 |

The data in Table 1 demonstrates that compounds of the present invention are potent inhibitors of interleukin 5 gene expression and therefore may have utility in the treatment of allergic diseases, in particular, asthma, chronic sinusitus, and chronic rhinitis.

Pharmaceutical Compositions

The present invention also provides pharmaceutical compositions which comprise compounds of the present invention formulated together with one or more non-toxic pharmaceutically acceptable carriers. The pharmaceutical compositions may be specially formulated for oral administration in solid or liquid form, for parenteral injection, or for rectal administration.

The term "pharmaceutically acceptable carrier," as used herein, means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing

agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator. The present invention provides pharmaceutical compositions which comprise compounds of the present invention formulated together with one or more non-toxic pharmaceutically acceptable carriers. Further included within the scope of the present invention are pharmaceutical compositions comprising one or more of the compounds of formula I-II prepared and formulated in combination with one or more non-toxic pharmaceutically acceptable compositions. The pharmaceutical compositions can be formulated for oral administration in solid or liquid form, for parenteral injection or for rectal administration.

The pharmaceutical compositions of this invention can be administered to humans and other mammals orally, rectally, parenterally , intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments or drops), bucally or as an oral or nasal spray. The term "parenterally," as used herein, refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous, intraarticular injection and infusion.

Pharmaceutical compositions of this invention for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity may be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservative agents, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include

isotonic agents, for example, sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Suspensions, in addition to the active compounds, may contain suspending agents, as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, tragacanth, and mixtures thereof.

If desired, and for more effective distribution, the compounds of the present invention can be incorporated into slow-release or targeted-delivery systems such as polymer matrices, liposomes, and microspheres. They may be sterilized, for example, by filtration through a bacteria-retaining filter or by incorporation of sterilizing agents in the form of sterile solid compositions, which may be dissolved in sterile water or some other sterile injectable medium immediately before use.

The active compounds can also be in micro-encapsulated form, if appropriate, with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound can be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may

optionally contain opacifying agents and can also be of such composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Injectable depot forms are made by forming microencapsulated matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides) Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic, parenterally acceptable diluent or solvent such as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; b) binders such as carboxymethylcellulose, alginates, gelatin,

polyvinylpyrrolidinone, sucrose, and acacia; c) humectants such as glycerol; d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; e) solution retarding agents such as paraffin; f) absorption accelerators such as quaternary ammonium compounds; g) wetting agents such as cetyl alcohol and glycerol monostearate; h) absorbents such as kaolin and bentonite clay; and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol,

tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Compounds of the present invention may also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes may be used. The present compositions in liposome form may contain, in addition to the compounds of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the natural and synthetic phospholipids and phosphatidylcholines (lecithins) used separately or together.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N. Y., (1976), p 33 et seq.

The compounds of the present invention, including but not limited to those specified in the examples, inhibit interleukin 5 gene expression. As IL-5 inhibitors, the compounds of the present invention may be useful for the treatment and prevention of allergic diseases such as asthma, chronic sinusitis, and chronic rhinitis.

When used in the above or other treatments, a therapeutically effective amount of one of the compounds of the present invention can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt form. Alternatively, the compound can be administered as a pharmaceutical composition containing the compound of interest in combination with one or more pharmaceutically acceptable excipients. The phrase "therapeutically effective amount" of the compound of the present invention means a sufficient amount of the compound to treat disorders, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgement. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active compound(s) that is effective to achieve the desired therapeutic response for a particular patient, compositions, and mode of

administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated, and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required for to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

The total daily dose of the compounds of this invention administered to a human or lower animal may range from about 0.003 to about 50 mg/kg/day. For purposes of oral administration, more preferable doses can be in the range of from about 0.01 to about 5 mg/kg/day. If desired, the effective daily dose can be divided into multiple doses for purposes of administration, e.g. two to four separate doses per day.

## Abbreviations

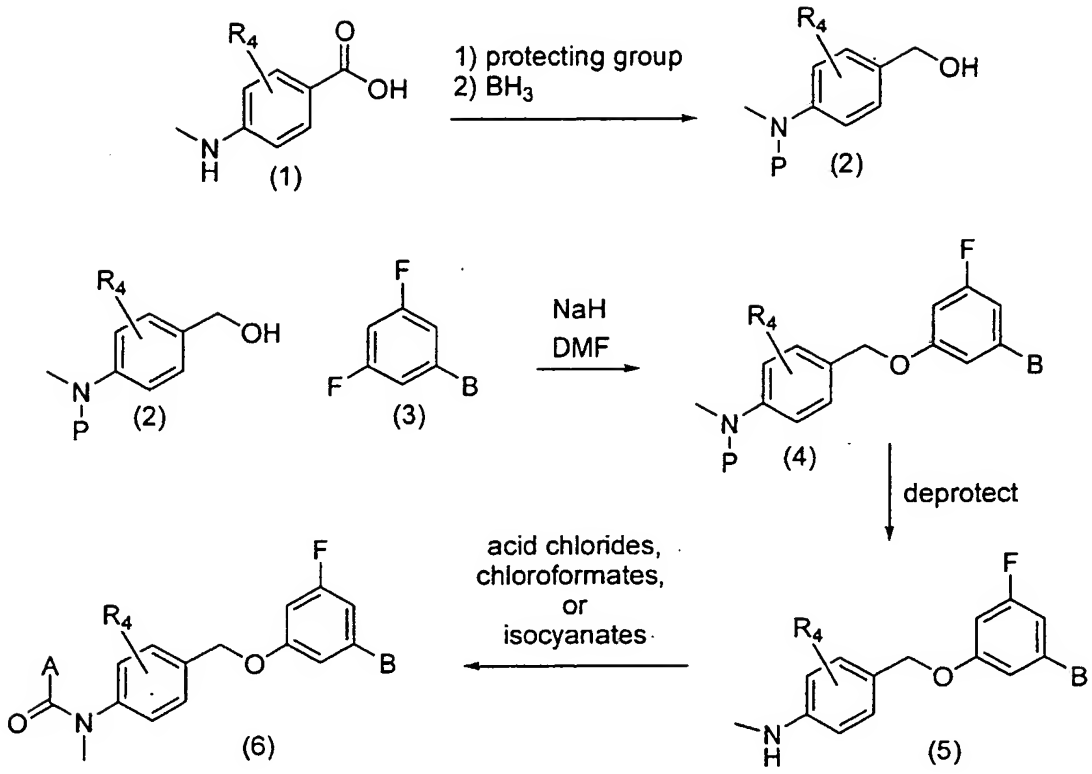
The following abbreviations are used: Ac for acetyl, BINAP for 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, Bn for benzyl, Boc for tert-butoxycarbonyl, $(Boc)_2O$ for di-tert-butyl dicarbonate, n-BuLi for n-butyllithium, dba for dibenzylideneacetone, DBAD for di-tert-butyl azodicarboxylate, DEAD for diethyl azodicarboxylate, DIAD for diisopropyl azodicarboxylate, DDQ for 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMF for dimethylformamide, DMSO for dimethylsulfoxide, dppf for 1,1'-bis(diphenylphosphino)ferrocene, EtOH for ethanol, eq for equivalent, Me for methyl, MeOH for methanol, EtOAc for ethyl acetate, TEA for triethylamine, $Tf_2O$ for trifluoromethanesulfonic anhydride, and THF for tetrahydrofuran.

## Preparation of Compounds of the Present Invention

The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes and methods which illustrate a means by which the compounds of the invention can be prepared.

The compounds of this invention can be prepared by a variety of synthetic routes. Representative procedures are shown in Schemes 1-12.

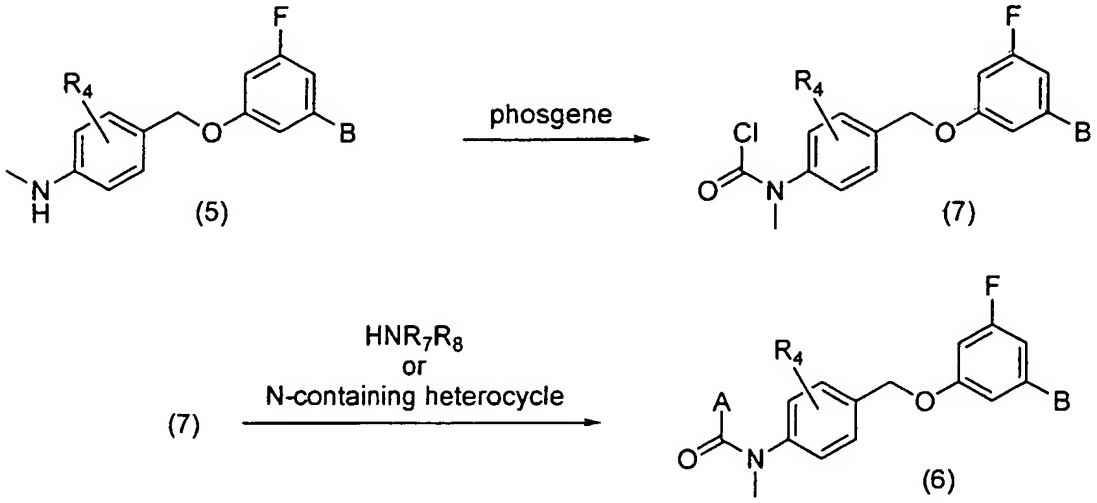
Scheme 1




Compounds of general formula (6), wherein B is an optionally substituted cyclohexyl group or an optionally substituted heterocycle and A and $R_4$ are as defined in formula I, can be prepared as described in Scheme 1. Benzoic acids of general formula (1), purchased or prepared using standard chemistry known to those of ordinary skill in the art, can be protected with a nitrogen protecting group, such as tert-butoxycarbonyl, by treating (1) with di-tert-butyl dicarbonate in 0.5M NaOH solution to provide N-protected benzoic acids. The N-protected benzoic acids can then be treated with a reducing agent, such as borane tetrahydrofuran complex or borane diethyl ether complex, to provide benzylic alcohols of general formula (2), wherein P is a nitrogen protecting group. Benzylic alcohols of general formula (2) can be treated with benzene compounds of general formula (3), prepared as described in Scheme 4, and sodium hydride to provide ethers of general formula (4). Ethers of general formula (4) can be deprotected by standard chemistry known to those of ordinary skill in the art to provide anilines of general formula (5). Anilines of general formula (5) can be treated with acid chlorides, chloroformates, or isocyanates under standard conditions

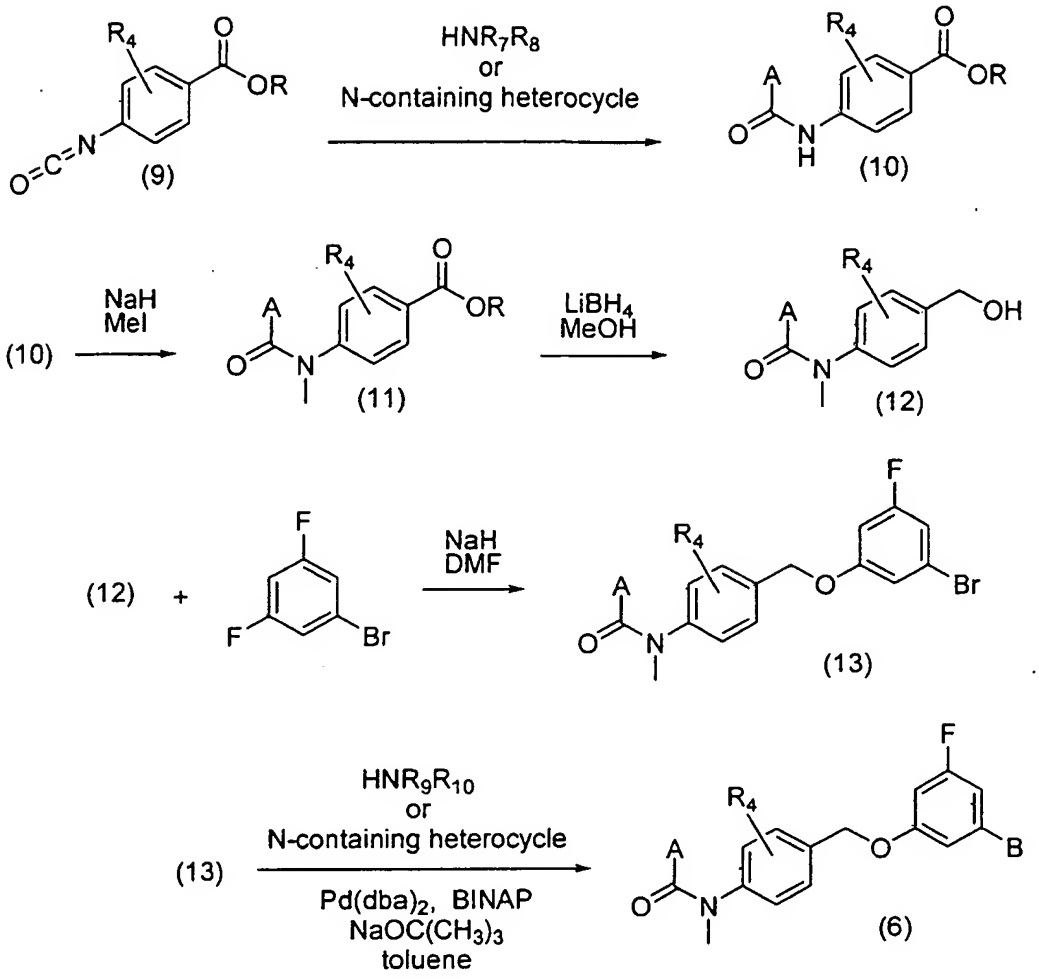
known to those of ordinary skill in the art to provide amides, carbamates, or ureas of general formula (6).

Scheme 2




Compounds of general formula (6), wherein A is selected from $NR_7R_8$ or nitrogen containing heterocycles such as azetidine, azocane, azepane, morpholine, piperdine, piperazine, pyrrole, pyrroline, pyrrolidine, thiazolidine, tetrahydropiperdine, and thiomorphoine, B is selected from cyclohexyl or heterocycle, and $R_4$, $R_7$, and $R_8$ are as defined in formula I, can be prepared as described in Scheme 2. Anilines of general formula (5), from Scheme 1, can be treated with phosgene in toluene at 0 °C to provide carbamoyl chlorides of general formula (7). Carbamoyl chlorides of general formula (7) can be treated with amines or nitrogen containing heterocycles to provide compounds of general formula (6) wherein A is an amine or nitrogen containing heterocycle and B is cyclohexyl or a heterocycle.

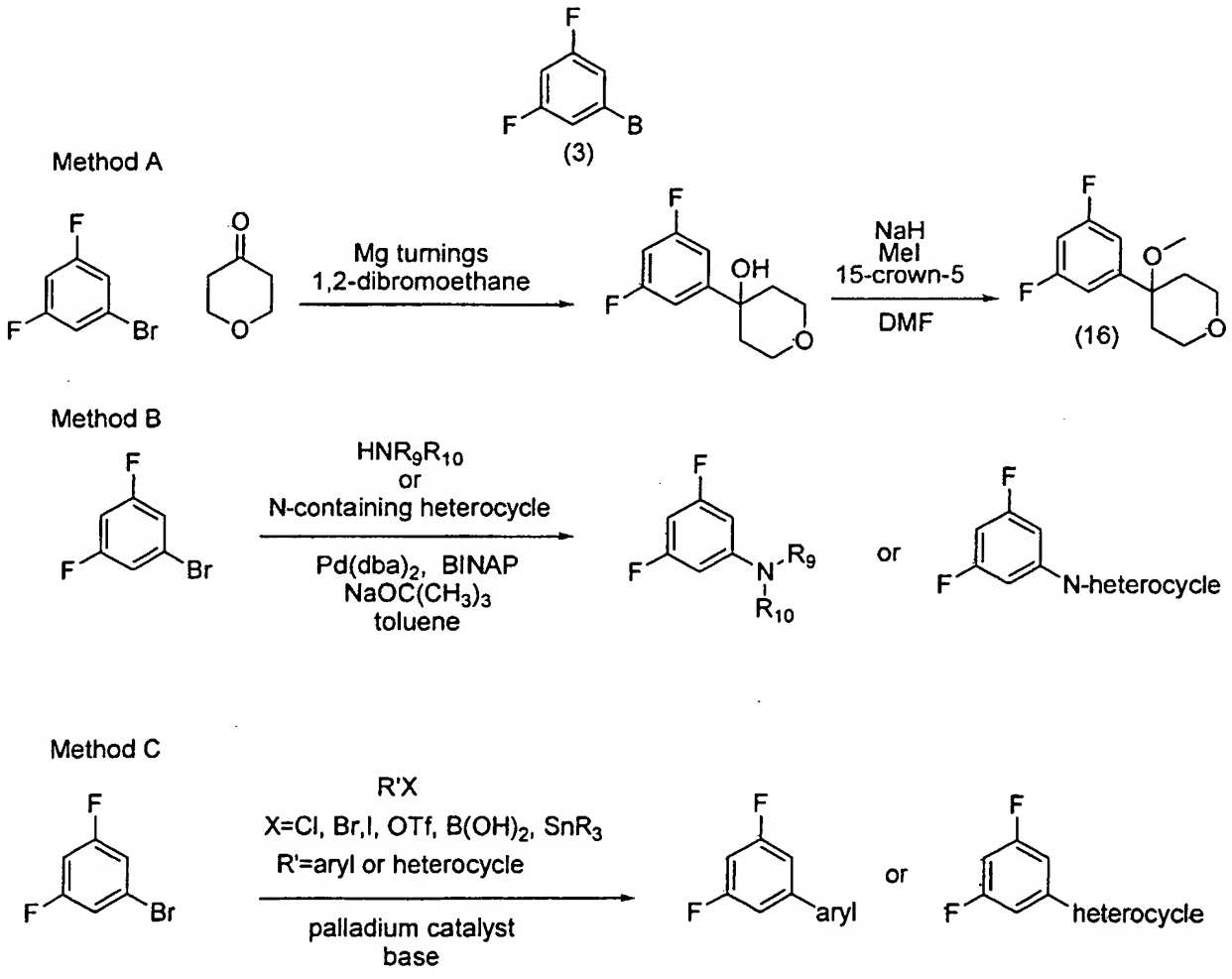
Scheme 3




Compounds of general formula (6), wherein A is selected from $NR_7R_8$ and nitrogen containing heterocycles such as azetidine, azocane, azepane, morpholine, piperdine, piperazine, pyrrole, pyrroline, pyrrolidine, thiazolidine, tetrahydropiperdine, and thiomorphoine, B is selected from $NR_9R_{10}$ and nitrogen containg heterocycles such as azetidine, azocane, azepane, morpholine, piperdine, piperazine, pyrrole, pyrroline, pyrrolidine, thiazolidine, tetrahydropiperdine, and thiomorphoine, and $R_4$, $R_7$, $R_8$, $R_9$, and $R_{10}$ are as defined in formula I, can be prepared as described in Scheme 3. Isocyanates of general formula (9) can be treated with amines or nitrogen containing heterocycles to provide compounds of general formula (10) wherein R is alkyl. Compounds of general formula (10) can be treated with sodium hydride and iodomethane in DMF to provide compounds of general formula (11). Compounds of general formula (11) can be treated with reducing

agents, such as lithium borohydride and methanol in THF, to provide alcohols of general formula (12). Alcohols of general formula (12) can be treated with 1-bromo-3,5-difluorobenzene to provide ethers of general formula (13). Ethers of general formula (13) can be treated with a palladium catalyst such as $Pd(dba)_2$, BINAP, and sodium tert-butoxide in toluene in the presence of an amine or nitrogen containing heterocycle to provide compounds of general formula (6) wherein A is an amine or nitrogen containing heterocycle and B is an amine or nitrogen containing heterocycle.

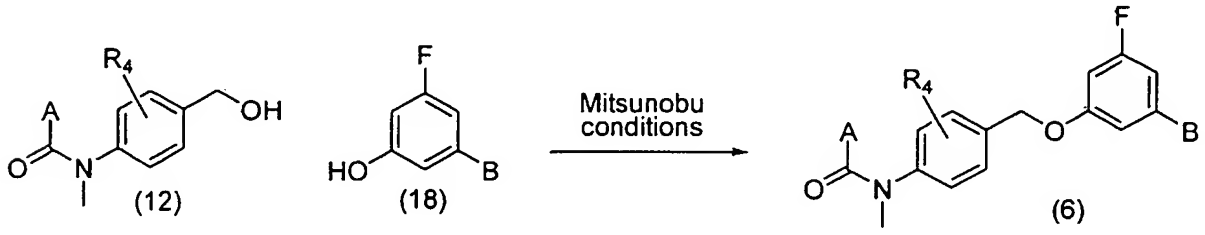
Scheme 4




Compounds of general formula (3), wherein B is as defined in formula I, can be prepared as described in Scheme 4. Method A is exemplified by describing the synthesis of

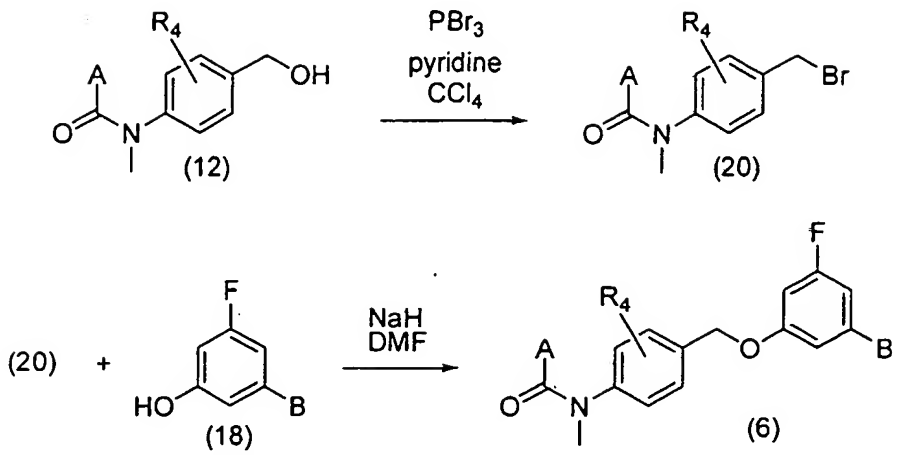
4-(3,5-difluorophenyl)-4-methoxytetrahydro-2H-pyran, (16). Cyclohexanones or heterocycles containing an oxo moiety, such as tetrahydro-4H-pyran-4-one, can be treated with the Grignard reagent prepared from 1-bromo-3,5-difluorobenzene, magnesium turnings, a catalytic amount of 1,2-dibromoethane, and an optional catalytic amount of iodine to provide alcohols such as 4-(3,5-difluorophenyl)tetrahydro-2H-pyran-4-ol. The alcohols can be treated with sodium hydride, iodomethane, and a catalytic amount of 15-crown-5 to provide 1-substituted-3,5-difluorobenzenes of general formula (3) such as 4-(3,5-difluorophenyl)-4-methoxytetrahydro-2H-pyran, (16). Method B demonstrates the replacement of bromine with amines and N-containing heterocycles using conditions as described in Scheme 3 or conditions described in (Wagaw, S. and Buchwald, S., J. Org. Chem. 61 (1996) 7240-7241; Harris, M.C. et al., J. Org. Chem. 64 (1999) 6019-6022). Method C demonstrates the replacement of bromine with aryl groups or heterocycles using well known Heck, Suzuki, or Stille chemistry as described in (Sharp, M.J. and Snieckus, V., Tet. Lett. 26 (1985) 5997; Syn. Commun., 11 (1981) 513; J. Org. Chem., 49 (1984) 5237; Tet. Lett., 28 (1987) 5093; Tet. Lett., 28 (1987) 5097; Bailey, T.R., Tet. Lett., 27 (1986) 4407; and Tet. Lett. 28 (1987) 2645).

Scheme 5



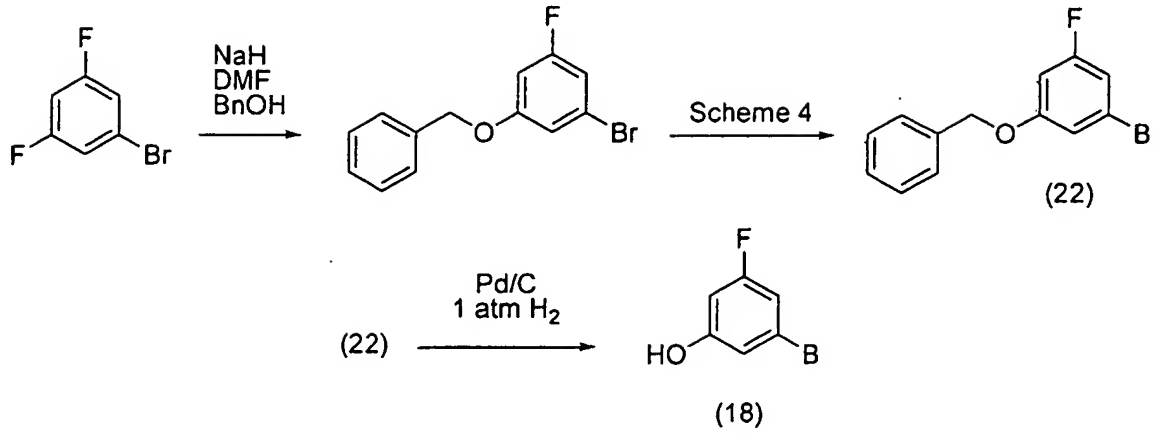

An alternate method of preparing compounds of general formula (6), wherein A is selected from $NR_7R_8$ and nitrogen containing heterocycles such as azetidine, azocane, azepane, morpholine, piperdine, piperazine, pyrrole, pyrroline, pyrrolidine, thiazolidine, tetrahydropiperdine, and thiomorphoine, and $R_4$, $R_7$, $R_8$, and B are as defined in formula I, is described in Scheme 5. Alcohols of general formula (12), from Scheme 3, can be treated with phenols of general formula (18), from Scheme 7, azo compounds such as DEAD, DBAD, and DIAD, and $PPh_3$ in a solvent such as THF to provide compounds of general formula (6).

Scheme 6



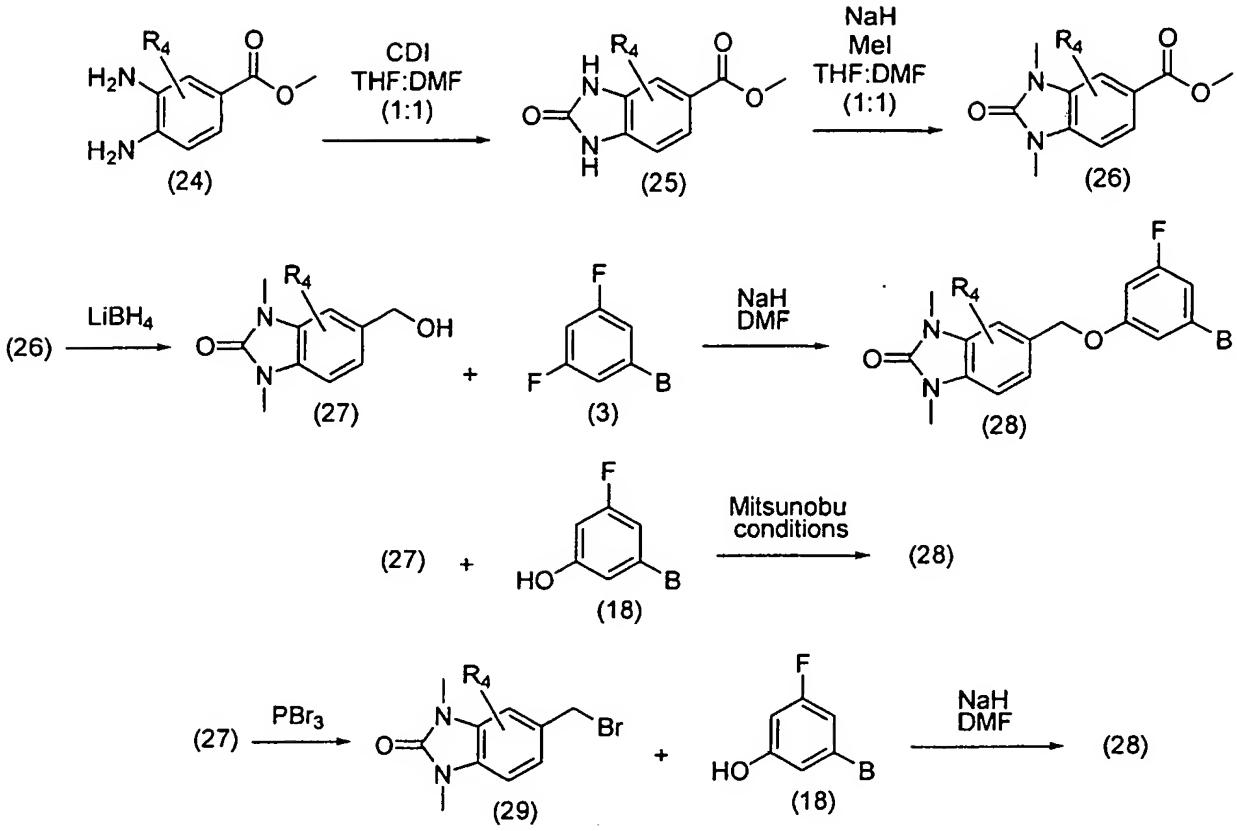

An alternate method of preparing compounds of general formula (6), wherein A is selected from $NR_7R_8$ and nitrogen containing heterocycles such as azetidine, azocane, azepane, morpholine, piperdine, piperazine, pyrrole, pyrroline, pyrrolidine, thiazolidine, tetrahydropiperdine, and thiomorpholine, and $R_4$, $R_7$, $R_8$, and B are as defined in formula I, is described in Scheme 6. Alcohols of general formula (12), from Scheme 3, can be treated with phosphorous tribromide and pyridine in carbon tetrachloride to provide bromomethyl compounds of general formula (20). Analogous chloromethyl compounds can also be prepared by treating alcohols of general formula (12) with phosphorous trichloride. Bromomethyl compounds of general formula (20) or the analogous chloromethyl compounds can be treated with phenols of general formula (18), from Scheme 7, and sodium hydride in DMF to provide compounds of general formula (6).

Scheme 7




Phenols of general formula (18), wherein B is as defined in formula I, can be prepared as described in Scheme 7. 1-Bromo-3,5-difluorobenzene can be treated with benzyl alcohol and sodium hydride in DMF to provide 1-(benzyloxy)-3-bromo-5-fluorobenzene. 1-(Benzyloxy)-3-bromo-5-fluorobenzene can be processed as described in Scheme 4 to provide compounds of general formula (22). Compounds of general formula (22) can be treated with a palladium catalyst such as 10% palladium on carbon under 1 atmosphere of hydrogen gas to provide phenols of general formula (18).

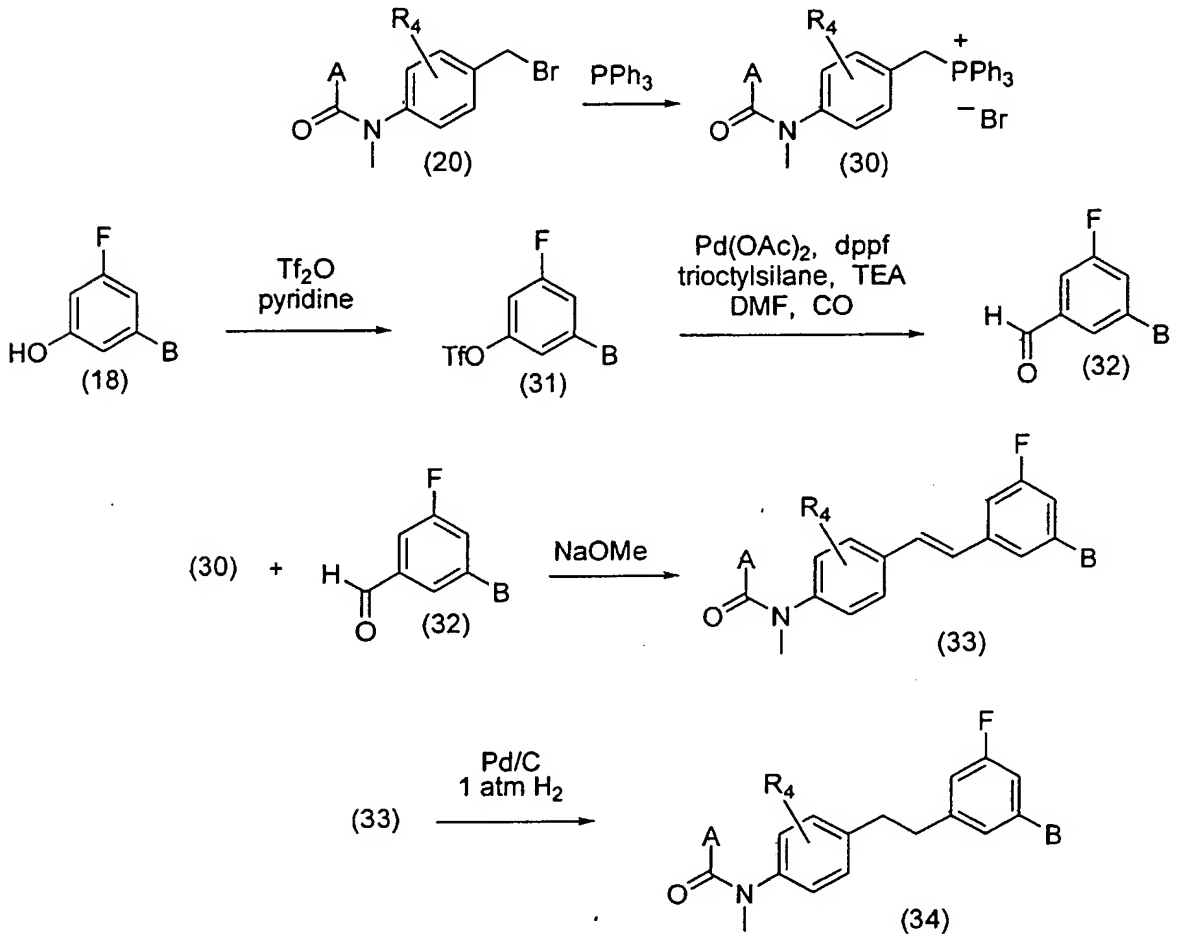
Scheme 8




Compounds of general formula (28), wherein $R_4$ and B are as defined in formula I, can be prepared as described in Scheme 8. Methyl 3,4-diaminobenzoates of general formula (24), purchased or prepared using standard chemistry known to those in the art, can be treated with 1,1'-carbonyldiimidazole to provide benzimidazoles of general formula (25). Benzimidazoles of general formula (25) can be dimethylated with sodium hydride and iodomethane, (26), and then treated with reducing agents such as lithium borohydride and MeOH in a solvent such as THF to provide alcohols of general formula (27). Alcohols of general formula (27) can be processed with benzenes of general formula (3), from Scheme 4, as described in Scheme 1 to provide compounds of general formula (28). Alternatively, alcohols of general formula (27) can be processed with phenols of general formula (18), from Scheme 7, using methodology described in Scheme 5 to provide compounds of general formula (28). Additionaly, alcohols of general formula (27) can be processed as described in Scheme 6 to provide bromides or chlorides of general formula (29). Bromomethyl

compounds of general formula (29) or the analogous chloromethyl can be processed with phenols of general formula (18), from Scheme 7, using methodology described in Scheme 6 to provide compounds of general formula (28).

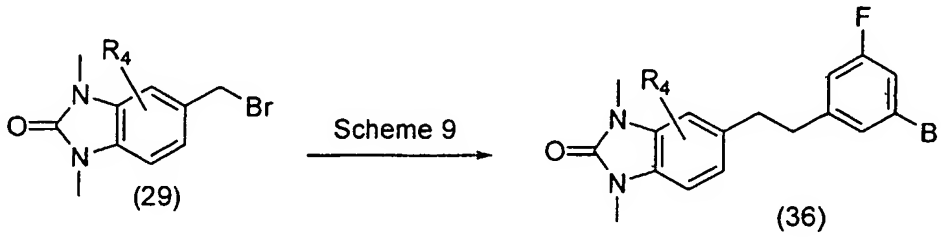
Scheme 9




Compounds of general formula (34), wherein A, B, and $R_4$ are as defined in formula I, can be prepared as described in Scheme 9. Bromides of general formula (20), from Scheme 6, or the analogous chlorides can be treated with triphenylphosphine in xylenes with heat to provide phosphonium salts of general formula (30). Phenols of general formula (18), from Scheme 7, can be treated with triflic anhydride in pyridine to provide triflates of general formula (31). Triflates of general formula (31) can be treated with a palladium catalyst such as palladium(II) acetate, dppf, trioctylsilane, a base such as triethylamine under an atmosphere of carbon monoxide to provide benzaldehydes of general formula (32).

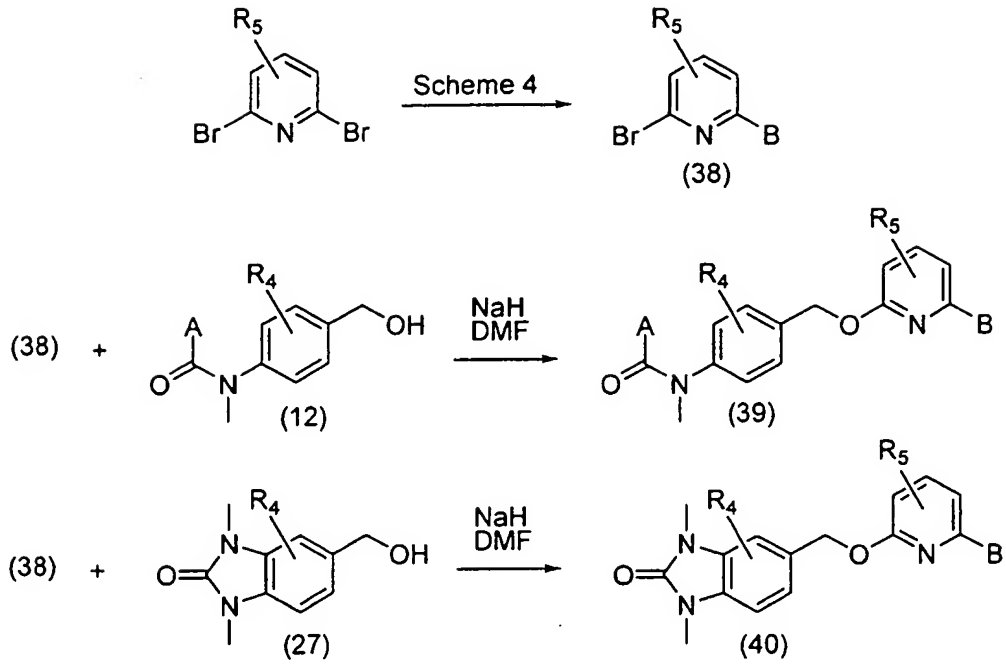
Phosphonium salts of general formula (30) can be treated with sodium methoxide and benzaldehydes of general formula (32) to provide alkenes of general formula (33). Alkenes of general formula (33) can be treated with a palladium catalyst such as 10% palladium on carbon under 1 atmosphere of hydrogen gas to provide compounds of general formula (34).

Scheme 10



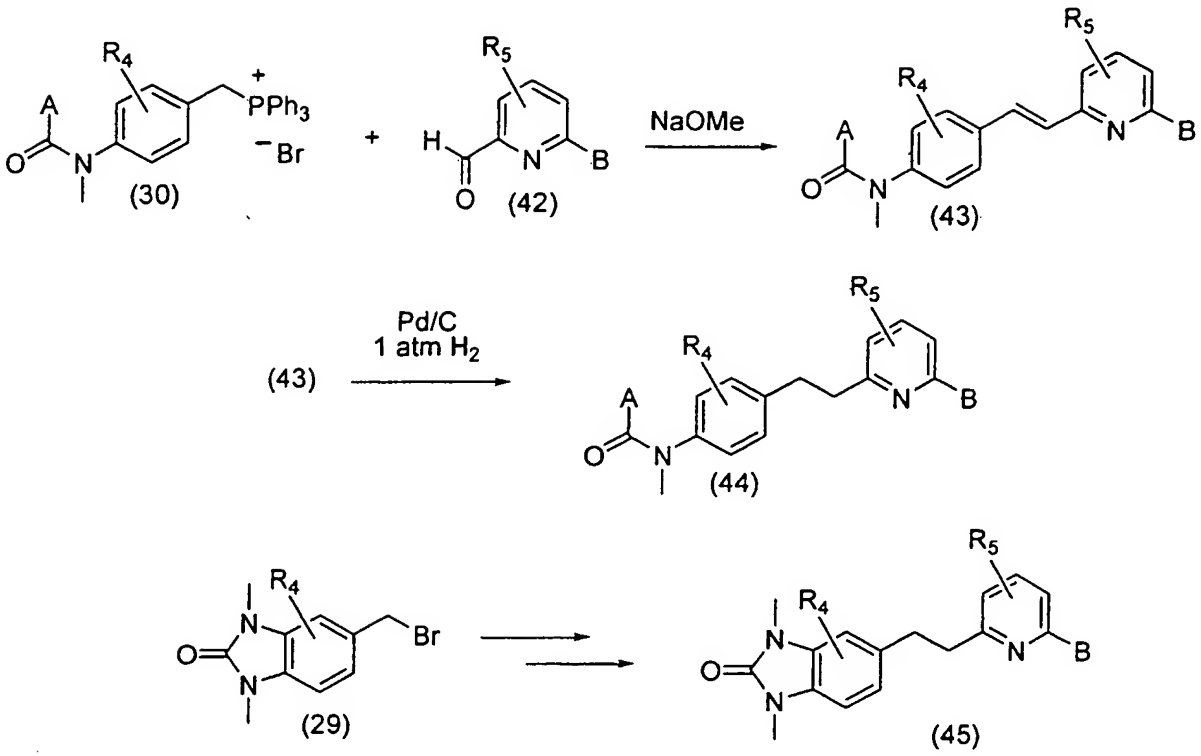

Compounds of general formula (36), wherein B and $R_4$ are as defined in formula I, can be prepared as described in Scheme 10. Bromomethyl compounds of general formula (29), from Scheme 8, or the analogous chloromethyl compounds can be processed as described in Scheme 9 to provide compounds of general formula (36).

Scheme 11




Compounds of general formula (39) and general formula (40), wherein A, B, $R_4$, and $R_5$ are as defined in formula I, can be prepared as described in Scheme 11. 2,6-Dibromopyridines or the analogous 2,6-dichloropyridines can be processed using the methods described in Scheme 4 to provide pyridines of general formula (38). Pyridines of general formula (38) can be treated with alcohols of general formula (12), from Scheme 3, and sodium hydride in DMF to provide compounds of general formula (39). Pyridines of general formula (38) can also be treated with alcohols of general formula (27), from Scheme 8, and sodium hydride in DMF to provide compounds of general formula (40).

Scheme 12




Compounds of general formula (44), wherein A, B, $R_4$, and $R_5$ are as defined in formula I, can be prepared as described in Scheme 12. Phosphonium salts of general formula (30), from Scheme 9, can be processed with 6-substituted-2-formylpyridines of general formula (42) as described in Scheme 9 to provide alkenes of general formula (43). Alkenes of general formula (43), can be reduced as described in Scheme 9 to provide compounds of general formula (44).

Compounds of general formula (45), wherein B, $R_4$, and $R_5$ are as defined in formula I, can also be prepared as described in Scheme 12. Bromomethyl compounds of general formula (29), from Scheme 8, or the analogous chloromethyl compounds can be processed as described in Scheme 9 and Scheme 12 to provide compounds of general formula (45).

The compounds and methods of the present invention will be better understood by reference to the following examples, which are intended as an illustration of and not a limitation upon the scope of the invention.

Example 1

ethyl 4-[3-({4-[[(diethylamino)carbonyl](methyl)amino]benzyl}oxy)-5-fluorophenyl]-1-piperazinecarboxylate

Example 1A

ethyl 4-isocyanatobenzoate

The title compound was purchased from Acros Organics.

Example 1B

ethyl 4-{[(diethylamino)carbonyl]amino}benzoate

The product from Example 1A and diethylamine were processed as described in Example 15A to provide the title compound.

Example 1C

ethyl 4-[[(diethylamino)carbonyl](methyl)amino]benzoate

The product from Example 1B was processed as described in Example 133B to provide the title compound.

Example 1D

N,N-diethyl-N'-[4-(hydroxymethyl)phenyl]-N'-methylurea

The product from Example 1C (3.5g, 13.26 mmol) in 100 mL of THF and 2 mL of MeOH was treated with lithium borohydride (1.5g, 68.8 mmol) and the reaction mixture was stirred overnight. After cooling on ice, the mixture was slowly quenched with saturated aqueous $NH_4Cl$ and extracted with ethyl acetate. The combined organic layers were washed with 1N HCl, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to provide 2.8 grams (89%) of the title compound as a solid. $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 0.82 (t, 6, J= 6), 3.0 (s, 3), 3.05 (q, 4, J= 7), 4.45 (d, 2, J= 6), 5.18 (t, 1, J= 6), 7.02 (d, 2, J= 7), 7.28 (d, 2, J= 8); MS (APCI+) m/z 237( $M+H)^+$.

Example 1E

N-{4-[(3-bromo-5-fluorophenoxy)methyl]phenyl}-N',N'-diethyl-N-methylurea

The product from Example 1D and 1-bromo-3,5difluorobenzene were processed as described in Example 15D to provide the title compound.

Example 1F

ethyl 4-[3-({4-[[(diethylamino)carbonyl](methyl)amino]benzyl}oxy)-5-fluorophenyl]-1-piperazinecarboxylate

The product from Example 1E (49 mg, 0.12 mmol) in 2.2 mL of dry degassed toluene was treated with ethyl 1-piperazinecarboxylate (2 equivalents), $Pd(dba)_2$ (7 mg, 0.01 mmol), BINAP (23 mg, 0.037 mmol), and sodium tert-butoxide (41 mg, 0.43 mmol). The mixture was kept at 80 °C for 15 hours and then allowed to cool to ambient temperature. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, and filtered through a silica gel sep-pak cartridge (Alltech 209150). The resulting solution was concentrated in vacuo to provide crude material. The crude residue was purified by preparative HPLC (Waters Nova-Pak® HR C18 6 μm 60 □ 25x100 mm, 50-95% MeCN/10 mM $NH_4OAc$ over 10 min at 40 mL/min) to provide 34.7 mg (59%) of the title compound as a light yellow oil. $^1H$ NMR (500 MHz, $CD_3OD$) δ 0.93 (t, 6, J=7.1), 1.27 (t, 3, J=7.1), 3.11-3.19 (m, 11), 3.59 (m, 4), 4.15 (q, 2, J=7.1), 5.04 (s, 2), 6.23 (dt, 1, J=10.6, 2.1), 6.31 (dt, 1, J=12.0, 2.1), 6.37 (m, 1), 7.13 (d, 2, J=8.7), 7.44 (d, 2, J=8.7); MS (APCI+) m/z 487 $(M+H)^+$.

Example 2

N-[4-({3-[bis(2-methoxyethyl)amino]-5-fluorophenoxy}methyl)phenyl]-N',N'-diethyl-N-methylurea

The product from Example 1E and N,N-bis(2-methoxyethyl)amine were processed as described in Example 1F to provide the title compound as a light yellow oil. $^1H$ NMR (500 MHz, $CD_3OD$) δ 0.93 (t, 6, J=7.1), 3.12 (s, 3), 3.14 (q, 4, J=7.1), 3.34 (s, 6), 3.51 (m, 8), 5.03

(s, 2), 6.03 (dt, 1, J=10.6, 2.2), 6.06 (dt, 1, J=12.7, 2.2), 6.11 (m, 1), 7.13 (d, 2, J=8.6), 7.43 (d; 2, J=8.6); MS (APCI+) m/z 462 $(M+H)^+$.

Example 3

N-(4-{[3-(2,6-dimethyl-4-morpholinyl)-5-fluorophenoxy]methyl}phenyl)-N',N'-diethyl-N-methylurea

The product from Example 1E and 2,6-dimethylmorpholine were processed as described in Example 1F to provide a cis:trans (4:1) mixture of the title compound as a light yellow oil. Cis isomer: $^1$H NMR (500 MHz, $CD_3OD$) δ 0.93 (t, 6, J=7.1), 1.21 (d, 6, J=6.2), 2.31 (dd, 2, J=12.2, 10.5), 3.12 (s, 3), 3.14 (q, 4, J=7.1), 3.49 (m, 2), 3.73 (m, 2), 5.04 (s, 2), 6.20 (dt, 1, J=10.4, 2.2), 6.28 (dt, 1, J=12.0, 2.2), 6.34 (m, 1), 7.13 (d, 2, J=8.5), 7.44 (d, 2, J=8.5). Trans isomer: $^1$H NMR (500 MHz, $CD_3OD$) δ 0.93 (t, 6, J=7.1), 1.26 (d, 6, J=6.5), 2.88 (dd, 2, J=12.0, 6.5), 3.12 (s, 3), 3.14 (q, 4, J=7.1), 3.20 (dd, 2, J=12.0, 3.3), 4.11 (m, 2), 5.04 (s, 2), 6.19 (dt, 1, J=10.4, 2.2), 6.25 (dt, 1, J=12.1, 2.2), 6.30 (m, 1), 7.13 (d, 2, J=8.5), 7.44 (d, 2, J=8.5); MS (APCI+) m/z 444 $(M+H)^+$.

Example 4

N,N-diethyl-N'-(4-{[3-fluoro-5-(4-thiomorpholinyl)phenoxy]methyl}phenyl)-N'-methylurea

The product from Example 1E and thiomorpholine were processed as described in Example 1 to provide the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.93 (t, 6, J=7.1), 2.65 (m, 4), 3.12 (s, 3), 3.14 (q, 4, J=7.1), 3.56 (m, 4), 5.04 (s, 2), 6.18 (dt, 1, J=10.5, 2.1), 6.25 (dt, 1, J=12.2, 2.1), 6.30 (m, 1), 7.13 (d, 2, J=8.3), 7.44 (d, 2, J=8.3); MS (APCI+) m/z 432 $(M+H)^+$.

Example 5

N,N-diethyl-N'-(4-{[3-fluoro-5-(4-hydroxy-1-piperidinyl)phenoxy]methyl}phenyl)-N'-methylurea

The product from Example 1E and 4-hydroxypiperdine were processed as described in Example 1F to provide the title compound as a yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ

0.93 (t, 6, J=7.1), 1.58 (m, 2), 1.92 (m, 2), 2.89 (ddd, 1, J=12.8, 10.3, 2.9), 3.12 (s, 3), 3.14 (q, 4, J=7.1), 3.55 (m, 2), 3.75 (m, 2), 5.03 (s, 2), 6.17 (dt, 1, J=10.6, 2.2), 6.28 (dt, 1, J=12.3, 2.2), 6.34 (m, 1), 7.13 (d, 2, J=8.5), 7.44 (d, 2, J=8.5); MS (APCI+) m/z 430 $(M+H)^+$.

Example 6

N-(4-{[3-(4-acetyl-1-piperazinyl)-5-fluorophenoxy]methyl}phenyl)-N',N'-diethyl-N-methylurea

The product from Example 1E and 1-acetylpiperazine were processed as described in Example 1F to provide the title compound as a pale yellow oil. $^1H$ NMR (500 MHz, $CD_3OD$) δ 0.93 (t, 6, J=7.1), 2.13 (s, 3), 3.12 (s, 3), 3.14 (q, 4, J=7.1), 3.16 (t, 2, J=5.2), 3.22 (t, 2, J=5.2), 3.66 (t, 2, J=5.2), 3.66 (t, 2, J=5.2), 5.04 (s, 2), 6.24 (dt, 1, J=10.5, 2.1), 6.32 (dt, 1, J=12.0, 2.1), 6.37 (m, 1), 7.13 (d, 2, J=8.4), 7.44 (d, 2, J=8.4); MS (APCI+) m/z 457 $(M+H)^+$.

Example 7

N,N-diethyl-N'-(4-{[3-fluoro-5-(1-piperidinyl)phenoxy]methyl}phenyl)-N'-methylurea

The product from Example 1E and piperdine were processed as described in Example 1F to provide the title compound as a yellow oil. $^1H$ NMR (500 MHz, $CD_3OD$) δ 0.93 (t, 6, J=7.1), 1.60 (m, 2), 1.67 (m, 4), 3.12 (s, 3), 3.14 (q, 4, J=7.1), 3.15 (m, 4), 5.03 (s, 2), 6.16 (dt, 1, J=10.5, 2.2), 6.26 (dt, 1, J=12.4, 2.2), 6.32 (m, 1), 7.13 (d, 2, J=8.6), 7.43 (d, 2, J=8.6); MS (APCI+) m/z 414 $(M+H)^+$.

Example 8

N-(4-{[3-(cyclopentylamino)-5-fluorophenoxy]methyl}phenyl)-N',N'-diethyl-N-methylurea

The product from Example 1E and cyclopentylamine were processed as described in Example 1F to provide the title compound as a light yellow-green oil. $^1H$ NMR (500 MHz, $CD_3OD$) δ 0.93 (t, 6, J=7.1), 1.46 (m, 2), 1.60 (m, 2), 1.72 (m, 2), 1.95 (m, 2), 3.12 (s, 3), 3.14 (q, 4, J=7.1), 3.69 (m, 1), 4.99 (s, 2), 5.95 (m, 2), 6.02 (m, 1), 7.12 (d, 2, J=8.7), 7.42 (d, 2, J=8.7); MS (APCI+) m/z 414 $(M+H)^+$.

Example 9

N-(4-{[3-(cyclohexylamino)-5-fluorophenoxy]methyl}phenyl)-N',N'-diethyl-N-methylurea

The product from Example 1E and cyclohexylamine were processed as described in Example 1F to provide the title compound as a light yellow-green oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.93 (t, 6, J=7.1), 1.11-1.45 (m, 6), 1.65 (m, 1), 1.77 (m, 2), 1.97 (m, 2), 3.12 (s, 3), 3.14 (q, 4, J=7.1), 4.99 (s, 2), 5.94 (m, 2), 6.01 (m, 1), 7.12 (d, 2, J=8.6), 7.42 (d, 2, J=8.6); MS (APCI+) m/z 428 $(M+H)^+$.

Example 10

N,N-diethyl-N'-[4-({3-fluoro-5-[4-(2-hydroxyethyl)-1-piperazinyl]phenoxy}methyl)phenyl]-N'-methylurea

The product from Example 1E and 1-(2-hydroxyethyl)piperazine were processed as described in Example 1F to provide the title compound as a colorless oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.93 (t, 6, J=7.1), 3.12 (s, 3), 3.15 (q, 4, J=7.1), 3.21 (br s, 2), 3.31 (m, 8), 3.89 (m, 2), 5.05 (s, 2), 6.32 (dt, 1, J=10.6, 2.1), 6.37 (dt, 1, J=11.7, 2.1), 6.42 (m, 1), 7.13 (d, 2, J=8.7), 7.44 (d, 2, J=8.7); MS (APCI+) m/z 459 $(M+H)^+$.

Example 11

N,N-diethyl-N'-(4-{[3-fluoro-5-(4-methyl-1-piperidinyl)phenoxy]methyl}phenyl)-N'-methylurea

The product from Example 1E and 4-methylpiperdine were processed as described in Example 1F to provide the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.93 (t, 6, J=7.1), 0.97 (d, 3, J=6.6), 1.27 (m, 2), 1.53 (m, 1), 1.72 (m, 2), 2.68 (dt, 2, J=12.4, 2.7), 3.12 (s, 3), 3.14 (q, 4, J=7.1), 3.63 (m, 2), 5.03 (s, 2), 6.16 (dt, 1, J=10.5, 2.2), 6.26 (dt, 1, J=12.4, 2.2), 6.33 (m, 1), 7.13 (d, 2, J=8.7), 7.43 (d, 2, J=8.7); MS (APCI+) m/z 428 $(M+H)^+$.

Example 12

N,N-diethyl-N'-[4-({3-[ethyl(2-methoxyethyl)amino]-5-fluorophenoxy}methyl)phenyl]-N'-methylurea

The product from Example 1E and ethyl(2-methoxyethyl)amine were processed as described in Example 1F to provide the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.93 (t, 6, J=7.1), 1.11 (t, 3, J=7.1), 3.12 (s, 3), 3.14 (q, 4, J=7.1), 3.35 (s, 3), 3.37 (q, 2, J=7.1), 3.43 (t, 2, J=5.6), 3.51 (t, 2, J=5.6), 5.03 (s, 2), 6.01 (m, 2), 6.07 (m, 1), 7.13 (d, 2, J=8.4), 7.43 (d, 2, J=8.4); MS (APCI+) m/z 432 $(M+H)^+$.

Example 13

N,N-diethyl-N'-(4-{[3-fluoro-5-(1-pyrrolidinyl)phenoxy]methyl}phenyl)-N'-methylurea

The product from Example 1E and pyrrolidine were processed as described in Example 1F to provide the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.92 (t, 6, J=7.1), 2.00 (m, 4), 3.12 (s, 3), 3.14 (q, 4, J=7.1), 3.22 (m, 4), 5.03 (s, 2), 5.89 (dt, 1, J=12.0, 2.2), 5.95 (m, 1), 5.99 (dt, 1, J=10.9, 2.2), 7.13 (d, 2, J=8.6), 7.43 (d, 2, J=8.6); MS (APCI+) m/z 400 $(M+H)^+$.

Example 14

N,N-diethyl-N'-(4-{[3-fluoro-5-(2-methyl-3-oxo-1-piperazinyl)phenoxy]methyl}phenyl)-N'-methylurea

The product from Example 1E and 3-methyl-2-piperazinone were processed as described in Example 1F to provide the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.93 (t, 6, J=7.1), 1.35 (d, 3, J=7.0), 3.12 (s, 3), 3.14 (q, 4, J=7.1), 3.34 (m, 2), 3.45 (m, 1), 3.58 (m, 1), 4.26 (q, 1, J=7.0), 5.05 (s, 2), 6.20 (dt, 1, J=10.6, 2.2), 6.25 (dt, 1, J=12.1, 2.2), 6.28 (m, 1), 7.13 (d, 2, J=8.7), 7.44 (d, 2, J=8.7); MS (APCI+) m/z 443 $(M+H)^+$.

Example 15

ethyl 4-{3-fluoro-5-[(4-{methyl[(2-methyl-1-pyrrolidinyl)carbonyl]amino}benzyl)oxy]phenyl}-1-piperazinecarboxylate

Example 15A

ethyl 4-{[(2-methyl-1-pyrrolidinyl)carbonyl]amino}benzoate

The product from Example 1A (3 g, 15.7 mmol) was treated with 1-methylpyrrolidine (1.34 g, 15.7 mmol) in 1mL of THF at 0 °C. After consumption of starting material was determined via TLC, the mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to provide 4.1 grams (95%) of the title compound as a white solid.

Example 15B

ethyl 4-{methyl[(2-methyl-1-pyrrolidinyl)carbonyl]amino}benzoate

The product from Example 15A was processed as described in Example 133B to provide the title compound.

Example 15C

N-[4-(hydroxymethyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide

The product from Example 15B was processed as described in Example 1D to provide the title compound.

Example 15D

N-{4-[(3-bromo-5-fluorophenoxy)methyl]phenyl}-N,2-dimethyl-1-pyrrolidinecarboxamide

The product from Example 15C (807 mg, 3.25 mmol) in 10 mL of DMF was treated with a suspension of NaH (126 mg, 5.25 mmol) in 5 mL of DMF and stirred at ambient temperature for 45 minutes to provide a yellowish, turbid solution. This solution was treated with 1-bromo-3,5-difluorobenzene (0.450 mL, 3.90 mmol) in 5 mL of DMF and stirred at ambient temperature for 4 hours. The mixture was quenched with 5% aqueous $NH_4Cl$ and extracted with ethyl acetate. The organic extracts were washed with 5% aqueous $NH_4Cl$, saturated aqueous $NaHCO_3$, water, brine, dried over anhydrous $Na_2SO_4$, and concentrated in vacuo to provide an oily yellow residue which was kept under vacuum at ambient

temperature for 48 hours. The residue was dissolved in ethyl acetate and filtered through a silica gel sep-pak cartridge (Alltech 239310). The solution was concentrated in vacuo to provide 1.26 grams (92%) of the title compound as a light yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, 3, J=6.2), 1.33 (m, 1), 1.64 (m, 2), 2.00 (m, 1), 2.61 (m, 1), 3.07 (m, 1), 3.24 (s, 3), 3.98 (m, 1), 4.98 (s, 2), 6.63 (dt, 1, J=10.5, 2.2), 6.87 (ddd, 1, J=8.0, 2.2, 1.6), 6.93 (m, 1), 7.13 (d, 2, J=8.4), 7.35 (d, 2, J=8.4); MS (APCI+) m/z 422/424 $(M+H)^+$.

Example 15E

ethyl 4-{3-fluoro-5-[(4-{methyl[(2-methyl-1-pyrrolidinyl)carbonyl]amino}benzyl)oxy]phenyl}-1-piperazinecarboxylate

The product from Example 15D (50 mg, 0.12 mmol), $Pd(dba)_2$ (7 mg, 0.01 mmol), BINAP (23 mg, 0.037 mmol), ethyl 1-piperazinecarboxylate (2 equivalents), and sodium tert-butoxide (40 mg, 0.42 mmol) were processed as described in Example 1F. The resulting residue was dissolved in ethyl acetate and filtered through a silica gel sep-pak cartridge (Alltech 209150). The filtrate was concentrated in vacuo and the crude residue was purified by preparative HPLC (Waters Nova-Pak® HR C18 6 μm 60 □ 25x100 mm, 50-95% MeCN/10 mM $NH_4OAc$ over 10 min at 40 mL/min) to provide 42.6 mg (72%) of the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.22 (d, 3, J=6.1), 1.27 (t, 3, J=7.1), 1.36 (m, 1), 1.59 (m, 1), 1.69 (m, 1), 2.00 (m, 1), 2.62 (m, 1), 3.09 (ddd, 1, J=10.5, 7.6, 3.1), 3.15 (m, 4), 3.19 (s, 3), 3.58 (m, 4), 3.88 (m, 1), 4.15 (q, 2, J=7.1), 5.04 (s, 2), 6.24 (dt, 1, J=10.5, 2.2), 6.32 (dt, 1, J=12.0, 2.2), 6.37 (m, 1), 7.16 (d, 2, J=8.4), 7.44 (d, 2, J=8.4); MS (APCI+) m/z 499 $(M+H)^+$.

Example 16

N-[4-({3-[bis(2-methoxyethyl)amino]-5-fluorophenoxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide

The product from Example 15D and N,N-bis(2-methoxyethyl)amine were processed as described in Example 15E to provide the title compound as a colorless oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.22 (d, 3, J=6.1), 1.36 (m, 1), 1.60 (m, 1), 1.69 (m, 1), 2.00 (m, 1), 2.62 (m,

1), 3.09 (ddd, 1, J=10.6, 7.5, 3.1), 3.19 (s, 3), 3.34 (s, 6), 3.51 (m, 8), 3.88 (m, 1), 5.02 (s, 2), 6.05 (m, 2), 6.12 (m, 1), 7.16 (d, 2, J=8.4), 7.43 (d, 2, J=8.4); MS (APCI+) m/z 474 $(M+H)^+$.

Example 17

N-(4-{[3-(2,6-dimethyl-4-morpholinyl)-5-fluorophenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide

The product from Example 15D and 2,6-dimethylmorpholine were processed as described in Example 15E to provide a (4:1) cis:trans mixture of the title compound as a light yellow oil. Cis isomer: $^1$H NMR (500 MHz, $CD_3OD$) δ 1.21 (d, 6, J=6.3), 1.22 (d, 3, J=6.1), 1.36 (m, 1), 1.60 (m, 1), 1.69 (m, 1), 2.00 (m, 1), 2.31 (m, 2), 2.61 (m, 1), 3.09 (ddd, 1, J=10.6, 7.5, 3.1), 3.19 (s, 3), 3.49 (m, 2), 3.74 (m, 2), 3.88 (m, 1), 5.03 (s, 2), 6.21 (dt, 1, J=10.6, 2.2), 6.29 (dt, 1, J=12.2, 2.2), 6.34 (m, 1), 7.16 (d, 2, J=8.6), 7.44 (d, 2, J=8.6). Trans isomer: $^1$H NMR (500 MHz, $CD_3OD$) δ 1.22 (d, 3, J=6.1), 1.26 (d, 6, J=6.4), 1.36 (m, 1), 1.60 (m, 1), 1.69 (m, 1), 2.00 (m, 1), 2.61 (m, 1), 2.88 (dd, 2, J=12.0, 6.2), 3.09 (ddd, 1, J=10.6, 7.5, 3.1), 3.19 (m, 2), 3.19 (s, 3), 3.88 (m, 1), 4.11 (m, 2), 5.03 (s, 2), 6.20 (dt, 1, J=10.6, 2.1), 6.26 (dt, 1, J=12.6, 2.1), 6.34 (m, 1), 7.16 (d, 2, J=8.6), 7.44 (d, 2, J=8.6); MS (APCI+) m/z 456 $(M+H)^+$.

Example 18

N-(4-{[3-fluoro-5-(4-thiomorpholinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide

The product from Example 15D and thiomorpholine were processed as described in Example 15E to provide the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.22 (d, 3, J=6.1), 1.37 (m, 1), 1.60 (m, 1), 1.69 (m, 1), 2.00 (m, 1), 2.62 (m, 1), 2.65 (m, 4), 3.09 (ddd, 1, J=10.6, 7.5, 3.1), 3.19 (s, 3), 3.56 (m, 4), 3.88 (m, 1), 5.03 (s, 2), 6.19 (dt, 1, J=10.5, 2.1), 6.26 (dt, 1, J=12.2, 2.1), 6.30 (m, 1), 7.16 (d, 2, J=8.3), 7.44 (d, 2, J=8.3); MS (APCI+) m/z 444 $(M+H)^+$.

Example 19

N-(4-{[3-fluoro-5-(4-hydroxy-1-piperidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide

The product from Example 15D and 4-hydroxypiperdine were processed as described in Example 15E to provide the title compound as a light yellow solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.22 (d, 3, J=6.1), 1.36 (m, 1), 1.53-1.65 (m, 3), 1.69 (m, 1), 1.92 (m,2), 2.01 (m, 1), 2.62 (m, 1), 2.89 (ddd, 1, J=12.9, 10.1, 2.9), 3.09 (ddd, 1, J=10.6, 7.6, 3.1), 3.19 (s, 3), 3.55 (m, 2), 3.75 (m, 1), 3.88 (m, 1), 5.03 (s, 2), 6.18 (dt, 1, J=10.5, 2.2), 6.29 (dt, 1, J=12.3, 2.2), 6.35 (m, 1), 7.16 (d, 2, J=8.6), 7.44 (d, 2, J=8.6); MS (APCI+) m/z 442 $(M+H)^+$.

Example 20

N-(4-{[3-(4-acetyl-1-piperazinyl)-5-fluorophenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide

The product from Example 15D and 1-acetylpiperazine were processed as described in Example 15E to provide the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.22 (d, 3, J=6.1), 1.36 (m, 1), 1.59 (m, 1), 1.68 (m, 1), 2.00 (m, 1), 2.13 (s, 3), 2.62 (m, 1), 3.09 (ddd, 1, J=10.5, 7.7, 3.0), 3.16 (t, 2, J=5.3), 3.19 (s, 3), 3.21 (t, 2, J=5.3), 3.66 (t, 2, J=5.3), 3.70 (t, 2, J=5.3), 3.88 (m, 1), 5.04 (s, 2), 6.25 (dt, 1, J=10.5, 2.2), 6.33 (dt, 1, J=12.0, 2.2), 6.38 (m, 1), 7.16 (d, 2, J=8.5), 7.44 (d, 2, J=8.5); MS (APCI+) m/z 469 $(M+H)^+$.

Example 21

N-(4-{[3-fluoro-5-(1-piperidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide

The product from Example 15D and piperdine were processed as described in Example 15E to provide the title compound as a yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.21 (d, 3, J=6.1), 1.36 (m, 1), 1.60 (m, 3), 1.67 (m, 5), 2.00 (m, 1), 2.61 (m, 1), 3.09 (ddd, 1, J=10.5, 7.6, 3.1), 3.14 (t, 4, J=5.5), 3.19 (s, 3), 3.88 (m, 1), 5.02 (s, 2), 6.17 (dt, 1, J=10.5,

2.1), 6.27 (dt, 1, J=12.4, 2.1), 6.33 (m, 1), 7.16 (d, 2, J=8.3), 7.44 (d, 2, J=8.3); MS (APCI+) m/z 426 $(M+H)^+$.

Example 22

N-[4-({3-fluoro-5-[4-(2-hydroxyethyl)-1-piperazinyl]phenoxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide

The product from Example 15D and 1-(2-hydroxyethyl)piperazine were processed as described in Example 15E to provide the title compound as a colorless oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.22 (d, 3, J=6.1), 1.36 (m, 1), 1.59 (m, 1), 1.69 (m, 1), 2.00 (m, 1), 2.57-2.65 (m, 3), 2.68 (m, 4), 3.09 (ddd, 1, J=10.6, 7.6, 3.1), 3.19 (s, 3), 3.20 (m, 4), 3.72 (t, 2, J=6.0), 3.88 (m, 1), 5.03 (s, 2), 6.22 (dt, 1, J=10.5, 2.1), 6.30 (dt, 1, J=12.2, 2.1), 6.35 (m, 1), 7.16 (d, 2, J=8.5), 7.44 (d, 2, J=8.5); MS (APCI+) m/z 471 $(M+H)^+$.

Example 23

N-(4-{[3-fluoro-5-(4-methyl-1-piperidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide

The product from Example 15D and 4-methylpiperdine were processed as described in Example 15E to provide the title compound as a yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.97 (d, 3, J=6.5),1.22 (d, 3, J=6.1), 1.30 (dq, 2, J=12.4, 4.0), 1.36 (m, 1), 1.48-1.74 (m, 5), 2.00 (m, 1), 2.61 (m, 1), 2.68 (dt, 2, J=12.4, 2.7), 3.09 (ddd, 1, J=10.5, 7.6, 3.1), 3.19 (s, 3), 3.68 (br d, 2, J=12.5), 3.88 (m, 1), 5.02 (s, 2), 6.17 (dt, 1, J=10.5, 2.1), 6.27 (dt, 1, J=12.4, 2.2), 6.33 (m, 1), 7.16 (d, 2, J=8.3), 7.43 (d, 2, J=8.3); MS (APCI+) m/z 440 $(M+H)^+$.

Example 24

N-[4-({3-[ethyl(2-methoxyethyl)amino]-5-fluorophenoxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide

The product from Example 15D and ethyl(2-methoxyethyl)amine were processed as described in Example 15E to provide the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.11 (d, 3, J=7.0), 1.21 (d, 3, J=6.1), 1.36 (m, 1), 1.60 (m, 1), 1.68 (m, 1),

2.00 (m, 1), 2.62 (m, 1), 3.09 (ddd, 1, J=10.6, 7.5, 3.0), 3.19 (s, 3), 3.34 (s, 3), 3.37 (q, 2, J=7.0), 3.43 (t, 2, J=5.8), 3.51 (t, 2, J=5.8), 3.88 (m, 1), 5.02 (s, 2), 6.02 (m, 2), 6.07 (m, 1), 7.16 (d, 2, J=8.5), 7.43 (d, 2, J=8.5); MS (APCI+) m/z 444 $(M+H)^+$.

Example 25

N-(4-{[3-fluoro-5-(1-pyrrolidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide

The product from Example 15D and pyrrolidine were processed as described in Example 15E to provide the title compound as a yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.21 (d, 3, J=6.1), 1.36 (m, 1), 1.59 (m, 1), 1.67 (m, 1), 2.00 (m, 5), 2.62 (m, 1), 3.09 (ddd, 1, J=10.5, 7.6, 3.1), 3.19 (s, 3), 3.22 (s, 4), 3.88 (m, 1), 5.02 (s, 2), 5.89 (dt, 1, J=12.0, 2.1), 5.95 (m, 1), 6.00 (dt, 1, J=10.9, 2.1), 7.15 (d, 2, J=8.5), 7.43 (d, 2, J=8.5); MS (APCI+) m/z 412 $(M+H)^+$.

Example 26

N-(4-{[3-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-5-fluorophenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide

The product from Example 15D and 1,4-dioxa-8-azaspiro[4.5]decane were processed as described in Example 15E to provide the title compound as a yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.21 (d, 3, J=6.1), 1.35 (m, 1), 1.60 (m, 1), 1.68 (m, 1), 1.75 (br t, 4, J=5.8), 2.00 (m, 1), 2.61 (m, 1), 3.09 (ddd, 1, J=10.6, 7.5, 3.1), 3.19 (s, 3), 3.30 (m, 4), 3.88 (m, 1), 3.96 (s, 4), 5.03 (s, 2), 6.18 (dt, 1, J=10.5, 2.1), 6.29 (dt, 1, J=12.3, 2.1), 6.34 (m, 1), 7.16 (d, 2, J=8.5), 7.43 (d, 2, J=8.5); MS (APCI+) m/z 484 $(M+H)^+$.

Example 27

N-(4-{[3-fluoro-5-(4-hydroxy-4-phenyl-1-piperidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide

The product from Example 15D and 4-hydroxy-4-phenylpiperdine were processed as described in Example 15E to provide the title compound as a yellow oil. $^1$H NMR (500 MHz,

$CD_3OD$) δ 1.21 (d, 3, J=6.1), 1.36 (m, 1), 1.59 (m, 1), 1.68 (m, 1), 1.80 (m, 2), 1.99 (m, 1), 2.16 (dt, 2, J=13.0, 4.4), 2.62 (m, 1), 3.08 (ddd, 1, J=10.6, 7.7, 3.2), 3.18 (s, 3), 3.23 (dt, 2, J=12.5, 2.5), 3.56 (m, 2), 3.88 (m, 1), 5.05 (s, 2), 6.20 (dt, 1, J=10.5, 2.2), 6.36 (dt, 1, J=12.3, 2.2), 6.41 (m, 1), 7.16 (d, 2, J=8.7), 7.23 (m, 1), 7.33 (m, 2), 7.45 (d, 2, J=8.7), 7.50 (m, 2); MS (APCI+) m/z 518 $(M+H)^+$.

Example 28

N-(4-{[3-fluoro-5-(3-hydroxy-1-pyrrolidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide

The product from Example 15D and 3-hydroxypyrrolidine were processed as described in Example 15E to provide the title compound as a yellow oil. $^1H$ NMR (500 MHz, $CD_3OD$) δ 1.22 (d, 3, J=6.1), 1.36 (m, 1), 1.59 (m, 1), 1.69 (m, 1), 2.00 (m, 2), 2.13 (m, 1), 2.62 (m, 1), 3.09 (ddd, 1, J=10.5, 7.6, 3.1), 3.15 (br d, 1, J=10.6), 3.19 (s, 3), 3.28 (dt, 1, J=8.8, 3.5), 3.36-3.46 (m, 2), 3.88 (m, 1), 4.50 (m, 1), 5.03 (s, 2), 5.90 (dt, 1, J=11.9, 2.1), 5.95 (m, 1), 6.02 (dt, 1, J=10.9, 2.1), 7.16 (d, 2, J=8.3), 7.44 (d, 2, J=8.3); MS (APCI+) m/z 428 $(M+H)^+$.

Example 29

N-[4-({3-fluoro-5-[4-(2-methoxyethyl)-1-piperazinyl]phenoxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide

The product from Example 15D and 1-(2-methoxyethyl)piperazine were processed as described in Example 15E to provide the title compound as a yellow oil. $^1H$ NMR (500 MHz, $CD_3OD$) δ 1.21 (d, 3, J=6.1), 1.36 (m, 1), 1.59 (m, 1), 1.68 (m, 1), 2.00 (m, 1), 2.62 (m, 1), 2.65 (t, 2, J=5.5), 2.68 (m, 4), 3.08 (ddd, 1, J=10.6, 7.6, 3.1), 3.19 (s, 3), 3.19 (m, 4), 3.35 (s, 3), 3.57 (t, 2, J=5.5), 3.88 (m, 1), 5.03 (s, 2), 6.22 (dt, 1, J=10.5, 2.1), 6.29 (dt, 1, J=12.1, 2.1), 6.34 (m, 1), 7.15 (d, 2, J=8.6), 7.44 (d, 2, J=8.6); MS (APCI+) m/z 485 $(M+H)^+$.

Example 30

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1-azocanecarboxamide

Example 30A

azocane hydrochloride

Azocane was purchased from Aldrich Chemical Co.

Example 30B

4-[(tert-butoxycarbonyl)(methyl)amino]benzoic acid

A solution of 4-(methylamino)benzoic acid (4.00 g, 26.5 mmol) in 60 mL of 0.5 M NaOH at 0° C was slowly treated with a solution of di(tert-butyl) dicarbonate (5.77 g, 2.65 mmol) in 60 mL of dioxane. After stirring at 0 °C for 30 minutes, the cold bath was removed and the pH adjusted to 12 with 1M NaOH. After stirring at ambient temperature for 2 hours, a second portion of di(tert-butyl) dicarbonate (5.77 g, 2.65 mmol) in 10 mL of dioxane was added and the pH adjusted to 12 with 1M NaOH. After stirring at ambient temperature for an additional 16 hours, the reaction mixture was concentrated in vacuo to half of the initial volume to provide a clear yellow solution. The solution was basified to pH 12 with 1M NaOH, washed with ethyl acetate, acidified to pH 2-3 with 10% aqueous $KHSO_4$, and extracted with ethyl acetate. The extracts were washed with 10% aqueous $KHSO_4$ and brine and evaporated to dryness to provide 5.60 grams (86%) of the title compound as a white solid. $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9), 3.32 (s, 3), 7.38 (d, 2, J= 8.7), 8.07 (d, 2, J= 8.7); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 28.2, 36.8, 81.2, 124.3, 125.5, 130.6, 148.6, 154.1, 171.5. MS (ESI-) m/z 250 $(M-H)^-$.

Example 30C

tert-butyl 4-(hydroxymethyl)phenyl(methyl)carbamate

A solution of the product from Example 30B (2.80 g, 11.1 mmol) in 45 mL of dry THF at 0°C was treated dropwise with a 1.0 M solution of borane diethyl etherate in THF

(45.0 mL, 45.0 mmol). After stirring at 0°C for 10 minutes, the reaction mixture was allowed to warm up slowly to ambient temperature. After stirring at ambient temperature for 3 hours, the reaction mixture was cooled in an ice bath and quenched with THF:water (1:1) and then water. The mixture was extracted with ethyl acetate and the combined extracts were washed with water and brine and evaporated in vacuo to provide 2.64 grams (100%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 9), 3.13 (s, 3), 4.50 (s, 2), 7.09 (d, 2, J=8.7), 7.22 (d, 2, J= 8.7); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 27.7, 37.0, 63.5, 80.2, 125.2, 126.9, 138.5, 142.3, 154.9; MS (ESI+) m/z 238 $(M+H)^+$.

Example 30D

4-(3,5-difluorophenyl)tetrahydro-2H-pyran-4-ol

The Grignard reagent prepared from magnesium metal (630 mg, 25.91 mmol), 5 drops of dibromoethane, and 3,5-difluorobromobenzene (5.00 g, 25.91 mmol) in 50 mL of diethyl ether was treated with tetrahydro-4H-pyran-4-one (2.40 mL, 25.91 mmol) in 25 mL of diethyl ether dropwise at ambient temperature. An additional 40 mL of diethyl ether was added and the reaction was allowed to stir at ambient temperature overnight. The reaction mixture was quenched with 150 mL of aqueous $NH_4Cl$ and extracted with diethyl ether (150 mL, 3X). The combined extracts were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The crude material was purified by column chromatography (0 to 2.5% $CH_3OH$ in $CH_2Cl_2$) to provide 3.74 grams (67%) of the title compound as a white solid. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.60 (d, 2, J=14.0), 2.06 (dt, 2, J=16.4, 6.8), 2.48 (br s, 1), 3.79-3.90 (m, 4), 6.69 (tt, 1, J=8.7, 2.3), 6.98 (d, 1, J=2.1), 7.00 (d, 1, J=2.1).

Example 30E

4-(3,5-difluorophenyl)-4-methoxytetrahydro-2H-pyran

The product from Example 30D (3.00 g, 14.0 mmol) and 10 drops of 15-crown-5 in 20 mL of DMF was treated with sodium hydride (1.96 g, 49.0 mmol) 60% dispersion in mineral oil prewashed with hexanes (20 mL, 4X). After stirring for 45 minutes at ambient temperature, the reaction mixture was treated with methyl iodide (3.5 mL, 56.0 mmol)

resulting in the formation of a white precipitate. An additional 10 mL of DMF was added and the reaction mixture was allowed to stir overnight. An additional 2 mL (32.1 mmol) of methyl iodide was added and after stirring for an additional 30 minutes, the mixture was carefully quenched with water and extracted with diethyl ether (150 mL, 3X). The combined extracts were washed with water, brine, dried over $Na_2SO_4$, and concentrated in vacuo. The crude material was purified using flash chromatography (5% ethyl acetate in hexanes) and then recrystalized from ethyl acetate/hexanes to provide 2.52 grams (79%) of the title compound as a white solid. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.88-2.03 (m, 4), 3.01 (s, 3), 3.84 (m, 4), 6.74 (tt, 1, J=8.6, 2.3 Hz), 6.91 (d, 1, J=2.4 Hz), 6.94 (d, 1, J=2.4 Hz).

Example 30F

tert-butyl 4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl(methyl)carbamate

The product from Example 30C (2.16 g, 9.10 mmol) in 10 mL of DMF was treated with sodium hydride (764 mg, 19.1 mmol), 60% in mineral oil, in portions. After stirring at ambient temperature for 45 minutes, the solution turned bright yellow. The bright yellow solution was treated with the product from Example 30E (1.09 g, 4.77 mmol) in 2.5 mL of DMF via cannula under positive $N_2$ pressure. The reaction mixture was heated to 90 °C for 3 hours, allowed to cool to ambient temperature, and then carefully quenched with water. The mixture was extracted with diethyl ether (75 mL, 3X) and the combined extracts were washed with water, brine, dried over $Na_2SO_4$, and concentrated in vacuo. The crude material was purified via flash chromatography ( 5 to 15% ethyl acetate in hexanes) to provide 1.02 grams (48%) of the title product: $^1$H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9), 1.88-2.03 (m, 4), 2.91 (s, 3), 3.27 (s, 3), 3.80-3.85 (m, 4), 5.02 (s, 2), 6.61 (d, 1H, J=10 Hz), 6.72 (d, 1, J=10 Hz), 6.81 (s, 1), 7.27 (app d, 2), 7.39 (d, 2, J=8.5 Hz); MS (ESI+) m/z 446 $(M+H)^+$.

Example 30G

4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}-N-methylaniline hydrochloride

The product from Example 30F (659 mg, 1.48 mmol) in 5 mL of dry dioxane was treated with 4M HCl in dioxane (15 mL). The mixture was stirred for 1 hour at ambient temperature. The solvent was removed in vacuo and the resultant oily yelllow residue was dried under vacuum at ambient temperature for 16 hours. The crude hydrochloride salt was used without further purification.

Example 30H

4-[3-({4-[(chlorocarbonyl)(methyl)amino]benzyl}oxy)-5-fluorophenyl]-4-methoxytetrahydro-2H-pyran

The crude product from Example 30G, suspended in 8 mL of dry toluene, was treated with triethylamine (0.740 mL, 5.31 mmol), stirred for 30 minutes at ambient temperature, and filtered. A vigorously stirred solution of phosgene (3.65 mL, 6.90 mmol) in 3 mL of toluene at 0 °C was slowly treated with the above filtrate via an addition funnel. After complete addition of the filtrate, the reaction mixture was stirred at 0 °C for 30 minutes and then allowed to warm up to ambient temperature. The solvent was removed in vacuo and the resultant yellow solid was suspended in 10 mL of THF and filtered to provide a solution of the title compound which was used immediately in preceding steps.

Example 30I

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1-azocanecarboxamide

In a 20-mL screw-cap vial, a freshly prepared solution of the product from Example 30H (one aliquot, equivalent to 43 mg of the carbamoyl chloride, 0.11 mmol) was treated with an excess of the product from Example 30A (about 10 equivalents). The resulting cloudy mixture was stirred at ambient temperature for 30 minutes. The mixture was partitioned between 5% aqueous $NH_4Cl$ and ethyl acetate. The organic layer was separated and washed with 5% aqueous $NH_4Cl$ and then water. The organic layer was filtered through a silica gel sep-pak cartridge (Alltech 209150) and concentrated in vacuo to provide a yellow oil. The crude material was purified by preparative HPLC (Waters Nova-Pak® HR C18 6 μm

60□ 25x100 mm, 50-95% MeCN/10mM $NH_4OAc$ over 10 minutes at 40 mL/minute) to provide 39.0 mg (59%) of the title compound as a pale yellow oil. $^1H$ NMR (500 MHz, $CDCl_3$) δ 1.51 (br s, 6), 1.60 (m, 4), 1.87-2.00 (m, 4), 2.98 (s, 3), 3.15 (m, 4), 3.17 (s, 3), 3.78-3.87 (m, 4), 5.00 (s, 2), 6.61 (dt, 1, J=10.3, 2.2), 6.72 (ddd, 1, J=9.9, 2.2, 1.5), 6.80 (m, 1), 7.04 (d, 2, J=8.6), 7.31 (d, 2, J=8.6); MS (APCI+) m/z 485 $(M+H)^+$.

Example 31

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-3-hydroxy-N-methyl-1-pyrrolidinecarboxamide

The product from Example 30H and 3-hydroxypyrrolidine were processed as described in Example 30I to provide 22.2 mg (35%) of the title compound as a colorless oil. $^1H$ NMR (500 MHz, $CDCl_3$) δ 1.76 (m, 1), 1.81-2.00 (m, 5), 2.98 (s, 3), 3.12 (br d, 1 J=11.7), 3.24 (s, 3), 3.24 (m, 3), 3.78-3.87 (m, 4), 4.32 (m, 1), 5.02 (s, 2), 6.62 (dt, 1, J=10.2, 2.2), 6.73 (br dt, 1, J=9.9, 1.7), 6.79 (m, 1), 7.16 (d, 2, J=8.1), 7.39 (d, 2, J=8.1); MS (APCI+) m/z 459 $(M+H)^+$.

Example 32

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide

The product from Example 30H and 2-methylpyrrolidine were processed as described in Example 30I to provide 35.0 mg (57%) of an oily, white solid. $^1H$ NMR (500 MHz, $CDCl_3$) δ 1.24 (d, 3, J=6.0), 1.34 (m, 1), 1.55-1.70 (m, 2), 1.87-2.03 (m, 5), 2.63 (m, 1), 2.98 (s, 3), 3.08 (m, 1), 3.24 (s, 3), 3.78-3.87 (m, 4), 3.98 (m, 1), 5.01 (s, 2), 6.62 (dt, 1, J=10.3, 2.2), 6.72 (ddd, 1, J=9.9, 2.2, 1.5), 6.81 (m, 1), 7.13 (d, 2, J=8.4), 7.38 (d, 2, J=8.2).

Example 33

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1-pyrrolidinecarboxamide

The product from Example 30H and pyrrolidine were processed as described in Example 30I to provide 32.0 mg (51%) of the title compound as a colorless oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.71 (m, 4), 1.90-2.01 (m, 4), 2.97 (s, 3), 3.06 (m, 4), 3.19 (s, 3), 3.74-3.87 (m, 4), 5.10 (s, 2), 6.70 (dt, 1, J=10.5, 2.3), 6.75 (dt, 1, J=10.1, 1.9), 6.85 (m, 1), 7.17 (d, 2, J=8.5), 7.46 (d, 2, J=8.5); MS (APCI+) m/z 443 $(M+H)^+$.

Example 34

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N',N'-trimethylurea

The title compound was prepared as described in US 5,432,194.

Example 35

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethyl-N'-propylurea

The product from Example 30H and N-methyl-N-propylamine were processed as described in Example 30I to provide 31.0 mg (52%) of the title compound as a yellow oily solid. $^1$H NMR (400 MHz, $CD_3OD$) δ 0.81 (t, 3, J=7.4), 1.46 (m, 2), 1.87-2.02 (m, 4), 2.61 (s, 3), 3.09 (m, 2), 2.96 (s, 3), 3.15 (s, 3), 3.73-3.86 (m, 4), 5.09 (s, 2), 6.69 (dt, 1, J=10.5, 2.3), 6.74 (ddd, 1, J=10.1, 2.3, 1.5), 6.84 (m, 1), 7.11 (d, 2, J=8.6), 7.45 (d, 2, J=8.6); MS (APCI+) m/z 445 $(M+H)^+$.

Example 36

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethylurea

Example 36A

4-{methyl[(methylamino)carbonyl]amino}benzoic acid

A suspension of 4-(methylamino)benzoic acid (756 mg, 5.0 mmol), purchased from Aldrich Chemical Co., in toluene (20 mL) was treated with a four-fold excess of methyl

isocyanate (1.2 mL, 20.0 mmol) at ambient temperature under a $N_2$ atmosphere. The mixture was heated to near reflux temperature (~100 °C). The reaction mixture was insoluble, anhydrous THF (5 mL) was added, and the mixture was heated to reflux for an additional 1 hour. After TLC showed no starting material remaining, the mixture was allowed to cool to ambient temperature and stirred overnight. The mixture was then filtered to provide the title compound (948 mg, 91% yield). mp 219-220 °C (dec., gas evolved); MS (DCI/$NH_3$) m/z 209 $(M+H)^+$, 226 $(M+NH_4)^+$.

Example 36B

N-[4-(hydroxymethyl)phenyl]-N,N'-dimethylurea

The product from Example 36A (948 mg, 4.55 mmol) and N-methylmorpholine (0.6 mL, 5.4 mmol) in anhydrous dimethoxyethane (10 mL) and anhydrous DMF (3.0 mL) was cooled in ice water and treated with isobutyl chloroformate (0.7 mL, 5.4 mmol). The mixture was stirred at 0 °C for 35 minutes and then allowed to warm to ambient temperature and stirred an additional 40 minutes. The mixture was filtered and the filtrate treated with sodium borohydride (800 mg, 21.0 mmol) and then poured over a mixture of ethyl acetate/saturated $NH_4Cl$. The ethyl acetate layer was separated, dried over $MgSO_4$, and concentrated to provide the title compound as a heavy colorless oil (550 mg) which began to crystallize. mp 71-87 °C (dec., gas evolved); MS (DCI/$NH_3$) m/z 195 $(M+H)^+$, 212 $(M+NH_4)^+$.

Example 36C

N-[4-(chloromethyl)phenyl]-N,N'-dimethylurea

The product from Example 36B (297 mg, 1.53 mmol) in anhydrous methylene chloride (15 mL) was treated with phosphorous trichloride (157 mg, 1.1 mmol) at -78 °C. The temperature was allowed to slowly rise to -20 °C. After stirring at -20 °C for 3 hours, saturated $NH_4Cl$ solution (15 mL) was added to the cold mixture followed by addition of solid $Na_2CO_3$ until the mixture reached pH = 8. The layers were shaken and separated. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to provide the title compound (122 mg).

Example 36D

3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenol

The title compound was prepared as described in WO 95/26346.

Example 36E

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethylurea

A suspension of NaH (80% suspension in mineral oil, 35 mg, 1.2 mmol) in DMF (2 mL) was treated with the product from Example 36D (226 mg, 1.0 mmol) in dry DMF (2 mL) at ambient temperature. After stirring at ambient temperature for 1 hour, the reaction mixture was treated with the product from Example 36C in dry DMF (1 mL). The mixture was diluted with a saturated $NH_4Cl$ solution and extracted with a hexane:diethyl ether mixture (1:1). The organic layer was dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (silica gel, $CH_2Cl_2$ to 15% ethyl acetate in $CH_2Cl_2$, and then 10 % MeOH in $CH_2Cl_2$) to provide the title compound (33.9 mg). MS (DCI/$NH_3$) m/z 403 $(M+H)^+$, 420 $(M+NH_4)^+$.

Example 37

N-allyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethylurea

The product from Example 133C, the product from Example 30E, and sodium hydride were processed as described in Example 30F to provide the title compound. MS (APCI+) m/z 443 $(M+H)^+$.

Example 38

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2,5-trimethyl-1-pyrrolidinecarboxamide

The product from Example 30H and 2,6-dimethylpyrrolidine were processed as described in Example 30I to provide 36.0 mg (57%) of the title compound as a yellow solid. $^1$H NMR (400 MHz, $CD_3OD$) δ 1.03 (d, 6, J=6.3), 1.56 (m, 2), 1.82 (m, 2), 1.89-2.02 (m, 4), 2.97 (s, 3), 3.12 (s, 3), 3.66 (m, 2), 3.74-3.87 (m, 4), 5.10 (s, 2), 6.69 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.0, 2.3, 1.5), 6.85 (m, 1), 7.12 (d, 2, J=8.7), 7.45 (d, 2, J=8.7); MS (APCI+) m/z 471 $(M+H)^+$.

Example 39

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-hydroxyethyl)-N,N'-dimethylurea

The product from Example 30H and 2-(methylamino)ethanol were processed as described in Example 30I to provide 12.0 mg (25%) of the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 1.88-2.01 (m, 4), 2.53 (s, 3), 2.99 (s, 3), 3.25 (s, 3), 3.41 (t, 2, J=4.8), 3.74-3.87 (m, 4), 3.77 (t, 2, J=4.8), 5.02 (s, 2), 6.61 (dt, 1, J=10.2, 2.2), 6.73 (dt, 1, J=9.8, 1.8), 6.81 (m, 1), 7.12 (d, 2, J=8.4), 7.41 (d, 2, J=8.4); MS (APCI+) m/z 447 $(M+H)^+$.

Example 40

N-(3-chloro-4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N',N'-trimethylurea

Example 40A

ethyl 4-amino-2-chlorobenzoate

4-Amino-2-chlorobenzoic acid (10.0 g, 58.2 mmol), purchased from Aldrich Chemical Co., and concentrated sulfuric acid (6.5 mL, 120 mmol) were combined in ethanol (150 mL) and refluxed for 1 hour. The reaction mixture was poured over ice and solid $K_2CO_3$ was added until pH=11. The mixture was filtered and the filtrate extracted with ethyl acetate. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to

provide the title compound (1.25 g) as a pale yellow solid. mp 103-107 °C; MS (DCI/$NH_3$) m/z 200 $(M+H)^+$.

Example 40B

ethyl 2-chloro-4-{[(methylamino)carbonyl]amino}benzoate

The product from Example 40A (1.25 g, 6.26 mmol) and methyl isocyanate (1.5 mL, 25.0 mmol) in toluene (25 mL) were heated at 100 °C for 2 hours. The reaction mixture was treated with additional methyl isocyanate (0.5 mL) and heated at 100 °C overnight. The mixture was cooled in an ice bath and filtered. The filter cake was washed with diethyl ether and dried in vacuo to provide (0.66 g) of the title compound as a solid. mp 146-148 °C; MS (DCI/$NH_3$) m/z 274 $(M+NH_4)^+$.

Example 40C

ethyl 2-chloro-4-[[(dimethylamino)carbonyl](methyl)amino]benzoate

The product from Example 40B (1.85 g, 7.20 mmol) in DMF was treated with 80% sodium hydride in mineral oil (540 mg, 18.0 mmol) at 0 °C. The mixture was allowed to warm to ambient temperature and stir for 30 minutes. The mixture was then recooled to 0 °C and treated with iodomethane (4.62 g, 30.0 mmol) and then allowed to warm to ambient temperature and stirred overnight. A solution of saturated $NH_4Cl$ was added and the mixture was extracted with diethyl ether:hexanes (1:1). The organic phase was dried ($MgSO_4$) and concentrated in vacuo to provide (1.89 g) of the title compound.

Example 40D

N-[3-chloro-4-(hydroxymethyl)phenyl]-N,N',N'-trimethylurea

The product from Example 40C was processed as described in Example 1D to provide the title compound.

Example 40E

N-[3-chloro-4-(chloromethyl)phenyl]-N,N',N'-trimethylurea

The product from Example 40D (512 mg, 2.11 mmol) in anhydrous methylene chloride (12 mL) was treated with phosphorous trichloride (320 mg, 2.33 mmol) at -40 °C. The temperature was allowed to slowly rise to -20 °C. After stirring at -20 °C for 3 hours, saturated $NaHCO_3$ solution and ethyl acetate were added and the layers separated. The organic layer was washed with water, brine, dried over $MgSO_4$ and concentrated in vacuo to provide the title compound (416 mg) as a yellow oil.

Example 40F

N-(3-chloro-4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N',N'-trimethylurea

The product from Example 40E (416 mg, 1.59 mmol), the product from Example 36D (386 mg, 1.71 mmol), and 80% sodium hydride in mineral oil (59 mg, 1.95 mmol) were processed as described in Example 36E to provide crude product. The residue was purified by flash chromatography (silica gel, $CH_2Cl_2$ to 25% ethyl acetate in $CH_2Cl_2$) to provide the title compound (425 mg) as a pale yellow oil. $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.9-2.04 (m, 4), 2.75 (s, 6), 2.98 (s, 3), 3.18 (s, 3), 3.72-3.88 (m, 4), 5.16 (s, 2), 6.7(dt, 1, J=10.6, 2.2), 6.76(dt, 1, J=12.0, 2.2), 6.85 (d, 1, J=2.2), 7.03 (dd, 1, J=9, J=1.5), 7.18 (d, 1, J=1.5), 7.54 (d, 1, J=9); MS (DCI/NH3) m/z 451 $(M+H)^+$; Analysis calculated for $C_{23}H_{28}ClFN_2O_4$: C, 61.26; H, 6.26; N, 6.21. Found: C, 60.90; H, 6.18; 6.19.

Example 41

(3R)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-3-hydroxy-N-methyl-1-pyrrolidinecarboxamide

The product from Example 30H and (3R)-3-pyrrolidinol were processed as described in Example 30I to provide 28.8 mg (45%) of the title compound as a white oily solid. $^1H$ NMR (500 MHz, $CD_3OD$) δ 1.73 (m, 1), 1.81 (m, 1), 1.90-2.00 (m, 4), 2.97 (s, 3), 3.03 (br d, 1, J=11.7), 3.12 (dd, 1, J=11.7, 4.6), 3.16-3.28 (m, 2), 3.20 (s, 3), 3.74-3.86 (m, 4), 4.21 (m, 1), 5.09 (s, 2), 6.70 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.85 (m, 1), 7.18 (d, 2, J=8.6), 7.46 (d, 2, J=8.6); MS (APCI+) m/z 459 $(M+H)^+$.

Example 42

3-ethyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2,4-trimethyl-1-pyrrolidinecarboxamide

The product from Example 30H and 3-ethyl-2,4-dimethylpyrrolidine were processed as described in Example 30I to provide 32.6 mg (47%) of the title compound as a mixture of isomers as a yellow oil. Major isomer: $^1$H NMR (500 MHz, $CD_3OD$) δ 0.81 (d, 3, J=6.5), 0.90 (t, 3, J=7.5), 1.10 (m, 1), 1.25 (d, 3, J=6.0), 1.39 (m, 1), 1.52 (m, 1), 1.66 (m, 1), 1.91-2.01 (m, 4), 2.19 (t, 1, J=10.8), 2.97 (s, 3), 3.20 (s, 3), 3.23 (dd, 1, J=10.6, 7.0), 3.58 (m, 1), 3.74-3.86 (m, 4), 5.10 (s, 2), 6.69 (dt, 1, J=10.5, 2.2), 6.74 (ddd, 1, J=10.3, 2.2, 1.5), 6.86 (m, 1), 7.16 (d, 2, J=8.6), 7.47 (d, 2, J=8.6); MS (APCI+) m/z 499 $(M+H)^+$.

Example 43

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2,5-trimethyl-2,5-dihydro-1H-pyrrole-1-carboxamide

The product from Example 30H and 2,5-dimethyl-2,5-dihydro-1H-pyrrole were processed as described in Example 30I to provide 29.2 mg (45%) of the title compound as a yellowish solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.22 (d, 6, J=6.3), 1.90-2.00 (m, 4), 2.97 (s, 3), 3.14 (s, 3), 3.74-3.85 (m, 4), 4.17 (q, 2, J=6.3), 5.08 (s, 2), 5.61 (s, 2), 6.69 (dt, 1, J=10.5, 2.2), 6.74 (ddd, 1, J=10.1, 2.2, 1.5), 6.85 (m, 1), 7.11 (d, 2, J=8.4), 7.45 (d, 2, J=8.4); MS (APCI+) m/z 469 $(M+H)^+$.

Example 44

N-(cyclopropylmethyl)-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methyl-N-propylurea

The product from Example 30H and N-(cyclopropylmethyl)-N-propylamine were processed as described in Example 30I to provide 29.0 mg (56%) of the title compound as an off white solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 0.12 (m, 2), 0.45 (m, 2), 0.77 (t, 3, J=7.4), 0.85 (m, 1), 1.44 (m, 1), 1.85-2.03 (m, 4), 2.98 (s, 3), 3.00 (d, 2, J=6.9), 3.10 (m, 2), 3.18 (s,

3), 3.83 (m, 4), 5.01 (s, 2), 6.61 (dt, 1, J=10.3, 2.2), 6.72 (ddd, 1, J=9.9, 2.2, 1.5), 6.81 (m, 1), 7.11 (d, 2, J=8.6), 7.37 (d, 2, J=8.6); MS (APCI+) m/z 485 $(M+H)^+$.

Example 45

N-ethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-isopropyl-N'-methylurea

The product from Example 30H and N-ethyl-N-isopropylamine were processed as described in Example 30I to provide 13.0 mg (27%) of the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 0.97 (d, 6, J=6.7), 1.05 (t, 3, J=7.0), 1.87-2.01 (m, 4), 2.98 (q, 2, J=7.0), 2.98 (s, 3), 3.16 (s, 3), 3.77-3.87 (m, 4), 4.08 (hept, 1, J=6.7), 5.01 (s, 2), 6.60 (dt, 1, J=10.3, 2.3), 6.72 (ddd, 1, J=9.9, 2.3, 1.5), 6.81 (m, 1), 7.10 (d, 2, J=8.5), 7.37 (d, 2, J=8.5); MS (APCI+) m/z 459 $(M+H)^+$.

Example 46

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethyl-N'-(2-propynyl)urea

The product from Example 30H and N-methyl-N-(2-propynyl)amine were processed as described in Example 30I to provide 27.0 mg (58%) of the title compound as a white solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 1.87-2.02 (m, 4), 2.63 (s, 3), 2.98 (s, 3), 3.24 (s, 3), 3.83 (m, 4), 3.09 (d, 2, J=2.6), 5.01 (s, 2), 6.62 (dt, 1, J=10.3, 2.3), 6.72 (m, 1), 6.85 (m, 1), 7.13 (d, 2, J=8.4), 7.40 (d, 2, J=8.4); MS (APCI+) m/e 441 $(M+H)^+$.

Example 47

N-(4-{2-[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenyl]ethyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide

Example 47A

N-[4-(bromomethyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide

The product from Example 15C was processed as described in Example 133D to provide the title compound.

Example 47B

(4-{methyl[(2-methyl-1-pyrrolidinyl)carbonyl]amino}benzyl)(triphenyl)phosphonium bromide

The product from Example 47A (0.225 g, 0.73 mmol) and triphenylphosphine (0.190 g, 0.73 mmol) in 15 mL of xylene were heated to reflux for 3 hours. The precipitate was filtered and washed with hexanes to provide 0.23 g (56%) of the title compound.

Example 47C

3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenyl trifluoromethanesulfonate

3-Fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenol (0.630 g. 2.77 mmol), prepared as described in WO 95/26346, in anhydrous pyridine (10 ml) was treated with trifluoromethanesulfonic anhydride (0.56 mL, ~1.2 eq) at 0 °C. The mixture was allowed to warm to ambient temperature and stirred for 1 hour. The reaction mixture was partitioned between 1N HCl and ethyl acetate. The organic layer was separated, washed with brine, dried ($MgSO_4$), and evaporated in vacuo to provide 0.93 g (93%) of 3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenyl trifluoromethanesulfonate as a reddish oil. MS (APCI+) m/z 359 $(M+H)^+$;

Example 47D

3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)benzaldehyde

The product from Example 47C (0.46 g. 1.27 mmol), $Pd(OAc)_2$ (0.006 g, 2 mol %), and dppf (0.011 g, 2 mol %), in DMF (10 mL) was heated at 70 °C for 20 minutes and then treated with triethylamine (0.42 mL, ~2.5 eq) dropwise followed with trioctylsilane (1.15 mL, ~2 eq). The reaction was stirred under an atmosphere of carbon monoxide for 2 hours. The resultant crude residue was purified by chromatography (silica gel, 15% ethyl acetate in

hexane) to provide the title compound (7 mg, 26%) as colorless oil. MS (APCI+) m/z 239 $(M+H)^+$.

Example 47E

N-(4-{-2-[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenyl]ethenyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide

The product from Example 47B (0.18 g, 0.31mmol) in 3 mL of dry MeOH was treated with sodium methoxide (0.094 mL 30 wt% in methanol) at ambient temperature. After stirring for 30 minutes, the product from Example 47D (0.075 g, 0.31 mmol) in 1 mL of MeOH was added dropwise. The mixture was stirred overnight and then partitioned between ethyl acetate and water. The combined organic phases were washed with brine and water, dried, and evaporated. The residue was purified by column chromatography on silica gel (55:45 hexanes:ethyl acetate) to provide 0.075g (54%) of the title compound. $^1$H NMR (500 MHz, $C_6D_6$) δ 0.84-1.04 (m, 3), 1.05-1.34 (m, 4), 1.42-1.8 (m, 4), 2.62 (s, 3), 2.70 (s, 3), 3.58-3.84 (m, 7), 6.31 (d, 1, J=12), 6.42 (d, 1, J=12), 6.8 (d, 1, J=8), 6.85 (d, 1, J=9), 6.88-6.94 (m, 1), 6.96-7.00 (m, 1), 7.04 (d, 1, J=8), 7.10 (s, 1), 7.2-7.4 (m, 1); MS (APCI+) m/z 453 ( $M+H)^+$.

Example 47F

N-(4-{2-[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenyl]ethyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide

The product from Example 47E (0.031 g, 0.069 mmol) in EtOH (2 mL) was treated with Pd/C (10%, 0.008 g) under an atmosphere of hydrogen, overnight. The mixture was then filtered through celite and silica gel and evaporated to provide 0.025 g (81%) of the desired compound. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 1.1 (d, 3, J=6), 1.2-1.3 (m, 1), 1.67 (m, 2), 1.8-1.95 (m, 5), 2.4-2.5 (m, 2), 2.85 (s, 3), 2.88-3.0 (m, 4), 3.02 (s, 3), 3.43-3.5 (m, 4), 3.7-3.8 (q, 1, J=7.5), 6.9-7.01 (m, 5), 7.15 (d, 2, J=9); MS (DCI/$NH_3$) m/z 455 $(M+H)^+$; Anal calcd for $C_{27}H_{35}FN_2O_4$: C, 71.33; H, 7.76; N, 6.16; found: C, 71.25; H, 8.01; N, 5.97.

Example 48

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-2,5-dihydro-1H-pyrrole-1-carboxamide

The product from Example 30H and 2,5-dihydro-1H-pyrrole were processed as described in Example 30I to provide 32.0 mg (51%) of the title compound as a colorless oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.89-2.00 (m, 4), 2.96 (s, 3), 3.21 (s, 3), 3.72-3.83 (m, 4), 3.85 (s, 4), 5.11 (s, 2), 5.67 (s, 2), 6.70 (dt, 1, J=10.5, 2.2), 6.75 (ddd, 1, J=10.1, 2.2, 1.5), 6.85 (m, 1), 7.21 (d, 2, J=8.6), 7.48 (d, 2, J=8.6); MS (APCI+) m/z 441 $(M+H)^+$.

Example 49

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1H-pyrrole-1-carboxamide

In a 50-mL flask, the product from Example 48 (59 mg, 0.13 mmol) was dissolved in 10 mL of dry ethyl acetate and solid DDQ (34 mg, 0.15 mmol) was added. The solution was refluxed for 6 hours. The resulting brown solution was washed with $H_2O$ and brine then filtered through a silica gel sep-pak cartridge (Alltech 209150). The solution was concentrated in vacuo to give the crude material as a brown oil. The crude oil was purified by preparative HPLC (Waters Nova-Pak® HR C18 6 μm 60 □ 25x100 mm, 50-95% MeCN/10 mM $NH_4OAc$ over 10 min at 40 mL/min) to provide 17.0 mg (29%) of the title compound as a yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.89-2.00 (m, 4), 2.96 (s, 3), 3.44 (s, 3), 3.74-3.86 (m, 4), 5.10 (s, 2), 5.98 (t, 2, J=2.4), 6.68 (dt, 1, J=10.6, 2.2), 6.75 (dt, 1, J=10.3, 2.2), 6.76 (t, 2, J=2.4), 6.84 (m, 1), 7.18 (d, 2, J=8.3), 7.45 (d, 2, J=8.3); MS (APCI+) m/z 407 $(M+H)^+$.

Example 50

N-(2-cyanoethyl)-N-cyclopropyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea

The product from Example 30H and 3-(cyclopropylamino)propanenitrile were processed as described in Example 30I to provide 30.0 mg (59%) of the title compound as a

colorless oily solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 0.50 (m, 2), 0.65 (m, 2), 1.87-2.02 (m, 5), 2.68 (t, 2, J= 6.5), 2.98 (s, 3), 3.27 (s, 3), 3.62 (t, 2, J= 6.5), 3.83 (m, 4), 5.01 (s, 2), 6.60 (dt, 1, J= 10.3, 2.2), 6.72 (dt, 1, J= 9.9, 1.8), 6.81 (m, 1), 7.24 (d, 2, J= 8.4), 7.41 (d, 2, J= 8.7); MS (APCI+) 482 $(M+H)^+$.

Example 51

N-allyl-N-ethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea

The product from Example 30H and N-allyl-N-ethylamine were processed as described in Example 30I to provide the title compound as a white solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, 3, J= 7.1), 1.87-2.01 (m, 4), 2.98 (s, 3), 3.13 (q, 2, J= 7.1), 3.17 (s, 3), 3.69 (br d, 2, J= 6.1), 3.83 (m, 4), 5.01 (s, 2), 5.03 (m, 1), 5.06 (m, 1), 5.56 (m, 1), 6.61 (dt, 1, J= 10.3, 2.3), 6.72 (dt, 1, J= 9.9, 1.8), 6.81 (m, 1), 7.12 (d, 2, J= 8.5), 7.39 (d, 2, J= 8.7); MS (APCI+) m/z 457 $(M+H)^+$.

Example 52

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-3-(hydroxymethyl)-N-methyl-1-piperidinecarboxamide

The product from Example 30H and 3-hydroxymethylpiperdine were processed as described in Example 30I to provide the title compound as a white oily solid. $^1$H NMR (400 MHz, $CD_3OD$) δ 1.17-1.35 (m, 2), 1.51 (m, 1), 1.68 (m, 2), 1.87-2.02 (m, 4), 2.85 (m, 1), 2.99 (s, 3), 3.04 (dd, 1, J= 13.3, 7.4), 3.23 (s, 3), 3.29 (m, 1), 3.43 (d, 2, J= 6.7); 3.48 (dd, 1, J= 13.3, 2.7); 3.77-3.88 (m, 4), 5.01 (s, 2), 6.61 (dt, 1, J= 10.1, 1.9), 6.72 (br d, 1, J= 9.9), 6.81 (m, 1), 7.11 (d, 2, J= 8.1), 7.39 (d, 2, J= 8.1); MS (APCI+) m/z 487 $(M+H)^+$.

Example 53

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1,3-thiazolidine-3-carboxamide

The product from Example 30H and 1,3-thiazolidine were processed as described in Example 30I to provide the title compound as a white solid. $^1$H NMR (400 MHz, $CD_3OD$) δ 1.87-2.02 (m, 4), 2.87 (br s, 2), 2.99 (s, 3), 3.26 (s, 3), 3.51 (t, 2, J=6.3), 3.77-3.88 (m, 4), 4.15 (br s, 2), 5.02 (s, 2), 6.62 (dt, 1, J=10.2, 2.3), 6.73 (ddd, 1, J=9.9, 2.3, 1.5), 6.81 (m, 1), 7.19 (d, 2, J=8.6), 7.42 (d, 2, J=8.6); MS (APCI+) m/z 461 $(M+H)^+$.

Example 54

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-methoxyethyl)-N,N'-dimethylurea

The product from Example 30H and N-(2-methoxyethyl)-N-methylamine were processed as described in Example 30I to provide the title compound as a colorless oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 1.88-2.03 (m, 4), 2.63 (s, 3), 2.98 (s, 3), 3.12 (s, 3), 3.33 (s, 3), 3.42 (t, 2, J=5.4), 3.48 (t, 2, J=5.4), 3.78-3.88 (m, 4), 5.00 (s, 2), 6.62 (dt, 1, J=10.3, 2.1), 6.75 (dt, 1, J=9.9, 1.7), 6.81 (m, 1), 7.11 (d, 2, J=8.3), 7.38 (d, 2, J=8.3); MS (APCI+) m/z 461 $(M+H)^+$.

Example 55

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-4-(hydroxymethyl)-N-methyl-1-piperidinecarboxamide

The product from Example 30H and 4-hydroxymethylpiperdine were processed as described in Example 30I to provide the title compound as a white oily solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 1.02 (br q, 2, J=12.4), 1.58 (m, 3), 1.87-2.02 (m, 4), 2.59 (br t, 2, J=12.4), 2.98 (s, 3), 3.22 (s, 3), 3.43 (d, 2, J=5.9), 3.78-3.89 (m, 6), 5.01 (s, 2), 6.61 (dt, 1, J=10.2, 2.1), 6.75 (dt, 1, J=9.9, 1.6), 6.80 (m, 1), 7.11 (d, 2, J=8.3), 7.38 (d, 2, J=8.3); MS (APCI+) m/z 487 $(M+H)^+$.

Example 56

N-ethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-(2-hydroxyethyl)-N'-methylurea

The product from Example 30H and 2-(ethylamino)ethanol were processed as described in Example 30I to provide the title compound as a white oily solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 0.74 (t, 2, J=7.1), 1.88-2.01 (m, 4), 2.99 (s, 3), 3.02 (q, 2, J=7.1), 3.20 (s, 3), 3.38 (t, 2, J=5.0), 3.73 (t, 2, J=5.0), 3.82 (m, 4), 5.03 (s, 2), 6.60 (dt, 1, J=10.3, 2.3), 6.72 (ddd, 1, J=9.9, 2.3, 1.5), 6.81 (m, 1), 7.14 (d, 2, J=8.5), 7.41 (d, 2, J=8.5); MS (APCI+) m/z 461 $(M+H)^+$.

Example 57

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-isopentyl-N,N'-dimethylurea

The product from Example 30H and N-isopentyl-N-methylamine were processed as described in Example 30I to provide the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 0.86 (d, 6, J=6.6), 1.32 (m, 2), 1.47 (m, 1), 1.86-2.03 (m, 4), 2.61 (s, 3), 2.98 (s, 3), 3.16 (m, 2), 3.20 (s, 3), 3.82 (m, 4), 5.00 (s, 2), 6.61 (dt, 1, J=10.3, 2.3), 6.72 (ddd, 1, J=9.9, 2.3, 1.5), 6.81 (m, 1), 7.08 (d, 2, J=8.6), 7.38 (d, 2, J=8.6); MS (APCI+) m/z 473 $(M+H)^+$.

Example 58

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-3-hydroxy-N-methyl-1-piperidinecarboxamide

The product from Example 30H and 3-hydroxypiperdine were processed as described in Example 30I to provide the title compound as a white solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 1.31 (m, 1), 1.50-1.77 (m, 3), 1.87-2.01 (m, 4), 2.99 (s, 3), 3.03 (m, 1), 3.12 (m, 1), 3.23 (m, 1), 3.22 (s, 3), 3.55 (m, 1), 3.70 (m, 1), 3.77-3.87 (m, 4), 5.01 (s, 2), 6.61 (dt, 1, J=10.3, 2.3), 6.73 (ddd, 1, J=9.9, 2.3, 1.5), 6.80 (m, 1), 7.13 (d, 2, J=8.5), 7.39 (d, 2, J=8.5); MS (APCI+) m/z 473 $(M+H)^+$.

Example 59

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-4-hydroxy-N-methyl-1-piperidinecarboxamide

The product from Example 30H and 4-hydroxypiperdine were processed as described in Example 30I to provide the title compound as a white solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 1.33 (m, 2), 1.71 (m, 2), 1.87-2.01 (m, 4), 2.89 (m, 2), 2.99 (s, 3), 3.22 (s, 3), 3.60 (m, 2), 3.75 (m, 1), 3.84 (m, 4), 5.01 (s, 2), 6.61 (dt, 1, J=10.3, 2.2), 6.72 (ddd, 1, J=9.9, 2.2, 1.5), 6.80 (m, 1), 7.12 (d, 2, J=8.6), 7.39 (d, 2, J=8.6); MS (APCI+) m/z 473 $(M+H)^+$.

Example 60

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-4-thiomorpholinecarboxamide

The product from Example 30H and thiomorpholine were processed as described in Example 30I to provide the title compound as a white solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 1.88-2.01 (m, 4), 2.40 (m, 4), 2.99 (s, 3), 3.21 (s, 3), 3.49 (m, 4), 3.83 (m, 4), 5.02 (s, 2), 6.61 (dt, 1, J=10.3, 2.3), 6.73 (ddd, 1, J=9.9, 2.3, 1.5), 6.81 (m, 1), 7.11 (d, 2, J=8.6), 7.41 (d, 2, J=8.6); MS (APCI+) m/z 475 $(M+H)^+$.

Example 61

N-[2-(1,3-dioxolan-2-yl)ethyl]-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethylurea

The product from Example 30H and N-[2-(1,3-dioxolan-2-yl)ethyl]-N-methylamine were processed as described in Example 30I to provide the title compound as a colorless oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 1.38 (m, 2), 1.87-2.01 (m, 4), 2.61 (s, 3), 2.98 (s, 3), 3.20 (s, 3), 3.32 (m, 2), 3.83 (m, 6), 3.93 (m, 2), 4.83 (t, 1, J=4.7), 5.00 (s, 2), 6.61 (dt, 1, J=10.3, 2.3), 6.72 (ddd, 1, J=9.9, 1.7, 0.5), 6.81 (m, 1), 7.09 (d, 2, J=8.4), 7.38 (d, 2, J=8.4); MS (APCI+) m/z 503 $(M+H)^+$.

Example 62

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-piperidinecarboxamide

The product from Example 30H and 2-methylpiperdine were processed as described in Example 30I to provide the title compound as a white solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.05 (d, 3, J= 6.9), 1.13-1.24 (m, 1), 1.39 (m, 2), 1.44-1.60 (m, 3), 1.89-2.02 (m, 4), 2.76 (dt, 1, J= 13.3, 2.9), 2.97 (s, 3), 3.15 (s, 3), 3.53 (br d, 1, J=13.3), 3.72-3.86 (m, 4), 4.22 (m, 1), 5.10 (s, 2), 6.68 (dt, 1, J=10.5, 2.3), 6.74 (ddd, 1, J=10.1, 2.3, 1.5), 6.85 (m, 1), 7.15 (d, 2, J=8.7), 7.45 (d, 2, J=8.7); MS (APCI+) m/z 471 $(M+H)^+$.

Example 63

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1-piperidinecarboxamide

The product from Example 30H and piperdine were processed as described in Example 30I to provide the title compound as a white solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.35 (m, 4), 1.50 (m, 2), 1.89-2.00 (m, 4), 2.97 (s, 3), 3.17 (s, 7), 3.74-3.86 (m, 4), 5.09 (s, 2), 6.69 (dt, 1, J=10.5, 2.2), 6.74 (ddd, 1, J=10.1, 2.2, 1.4), 6.84 (m, 1), 7.13 (d, 2, J=8.5), 7.45 (d, 2, J=8.5); MS (APCI+) m/z 457 $(M+H)^+$.

Example 64

N-ethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethylurea

The product from Example 30H and N-ethyl-N-methylamine were processed as described in Example 30I to provide the title compound as a colorless oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.00 (t, 3, J= 7.2), 1.87-2.07 (m, 4), 2.59 (s, 3), 2.97 (s, 3), 3.16 (s, 3), 3.21 (q, 2, J=7.2), 3.73-3.86 (m, 4), 5.09 (s, 2), 6.69 (dt, 1, J=10.5, 2.2), 6.74 (ddd, 1, J=10.1, 2.2, 1.5), 6.84 (m, 1), 7.12 (d, 2, J=8.3), 7.45 (d, 2, J=8.3); MS (APCI+) m/z 431 $(M+H)^+$.

Example 65

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-3,6-dihydro-1(2H)-pyridinecarboxamide

The product from Example 30H and 1,2,3,6-tetrahydropyridine were processed as described in Example 30I to provide the title compound as a colorless oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.85-2.01 (m, 6), 2.97 (s, 3), 3.19 (s, 3), 3.33 (t, 2, J= 5.7), 3.58 (m, 2), 3.74-3.86 (m, 4), 5.10 (s, 2), 5.53 (m, 1), 5.72 (m, 1), 6.69 (dt, 1, J=10.5, 2.3), 6.74 (ddd, 1, J=10.1, 2.3, 1.5), 6.84 (m, 1), 7.16 (d, 2, J=8.7), 7.46 (d, 2, J=8.7); MS (APCI+) m/z 455 $(M+H)^+$.

Example 66

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1-azepanecarboxamide

The product from Example 30H and azepane were processed as described in Example 30I to provide the title compound as a light yellow solid. $^1$H NMR (400 MHz, $CD_3OD$) δ 1.50 (m, 4), 1.57 (m, 4), 1.87-2.01 (m, 4), 2.97 (s, 3), 3.19 (s, 3), 3.18 (m, 4), 3.72-3.87 (m, 4), 5.09 (s, 2), 6.69 (dt, 1, J=10.5, 2.3), 6.74 (ddd, 1, J=10.1, 2.3, 1.5), 6.84 (m, 1), 7.10 (d, 2, J=8.7), 7.44 (d, 2, J=8.7); MS (APCI+) m/z 471 $(M+H)^+$.

Example 67

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-4-(2-hydroxyethyl)-N-methyl-1-piperidinecarboxamide

The product from Example 30H and 2-(4-piperidinyl)ethanol were processed as described in Example 30I to provide the title compound as a light yellow solid. $^1$H NMR (400 MHz, $CD_3OD$) δ 0.97 (br dt, 2, J= 12.3, 2.8), 1.39 (q, 2, J= 6.6), 1.46-1.59 (m, 3), 1.90-2.03 (m, 4), 2.60 (dt, 2, J=12.9, 2.1), 2.97 (s, 3), 3.17 (s, 3), 3.54 (t, 2, J=6.6), 3.73-3.87 (m, 6), 5.09 (s, 2), 6.68 (dt, 1, J=10.5, 2.3), 6.74 (ddd, 1, J=10.1, 2.3, 1.5), 6.85 (m, 1), 7.13 (d, 2, J=8.6), 7.45 (d, 2, J=8.6); MS (APCI+) m/z 501 $(M+H)^+$.

Example 68

N,N-diallyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea

The product from Example 30H and N,N-diallylamine were processed as described in Example 30I to provide the title compound as a bright yellow solid. $^1$H NMR (400 MHz, $CD_3OD$) δ 1.87-2.02 (m, 4), 2.97 (s, 3), 3.14 (s, 3), 3.67 (br d, 4, J=6.0), 3.73-3.87 (m, 4), 5.04 (m, 4), 5.11 (s, 2), 5.46-5.59 (m, 2), 6.69 (dt, 1, J=10.5, 2.3), 6.74 (ddd, 1, J=10.1, 2.3, 1.5), 6.85 (m, 1), 7.17 (d, 2, J=8.5), 7.47 (d, 2, J=8.5); MS (APCI+) m/z 469 $(M+H)^+$.

Example 69

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N',N'-dipropylurea

The product from Example 30H and N,N-dipropylamine were processed as described in Example 30I to provide the title compound as a yellow oily solid. $^1$H NMR (400 MHz, $CD_3OD$) δ 0.77 (t, 6, J= 8.4), 1.41 (m, 4), 1.87-2.03 (m, 4), 2.97 (s, 3), 3.02 (m, 4), 3.13 (s, 3), 3.74-3.87 (m, 4), 5.10 (s, 2), 6.69 (dt, 1, J=10.5, 2.3), 6.74 (ddd, 1, J=10.1, 2.3, 1.5), 6.85 (m, 1), 7.14 (d, 2, J=8.6), 7.45 (d, 2, J=8.6); MS (APCI+) m/z 473 $(M+H)^+$.

Example 70

N-butyl-N-ethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea

The product from Example 30H and N-butyl-N-ethylamine were processed as described in Example 30I to provide the title compound as a yellow solid. $^1$H NMR (400 MHz, $CD_3OD$) δ 0.84 (t, 3, J=7.3), 0.96 (t, 3, J=7.1), 1.17 (m, 2), 1.34 (m, 2), 1.87-2.01 (m, 4), 2.97 (s, 3), 3.04 (m, 2), 3.13 (s, 3), 3.15 (q, 2, J=7.1), 3.73-3.88 (m, 4), 5.09 (s, 2), 6.69 (dt, 1, J=10.5, 2.3), 6.74 (ddd, 1, J=10.1, 2.3, 1.5), 6.85 (m, 1), 7.13 (d, 2, J=8.6), 7.46 (d, 2, J=8.6); MS (APCI+) m/z 473 $(M+H)^+$.

Example 71

N-ethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methyl-N-propylurea

The product from Example 30H and N-ethyl-N-propylamine were processed as described in Example 30I to provide the title compound as a bright yellow solid. $^1$H NMR (400 MHz, $CD_3OD$) δ 0.75 (t, 3, J=7.4), 0.95 (t, 3, J=7.1), 1.39 (m, 2), 1.87-2.02 (m, 4), 2.97 (s, 3), 3.00 (m, 2), 3.13 (s, 3), 3.15 (q, 2, J=7.2), 3.73-3.87 (m, 4), 5.10 (s, 2), 6.69 (dt, 1, J=10.5, 2.3), 6.74 (ddd, 1, J=10.0, 2.3, 1.5), 6.85 (m, 1), 7.14 (d, 2, J=8.7), 7.46 (d, 2, J=8.7); MS (APCI+) m/z 459 $(M+H)^+$.

Example 72

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-isopropyl-N,N'-dimethylurea

The product from Example 30H and N-isopropyl-N-methylamine were processed as described in Example 30I to provide the title compound as a bright yellow solid. $^1$H NMR (400 MHz, $CD_3OD$) δ 1.02 (d, 6, J=6.8), 1.88-2.03 (m, 4), 2.43 (s, 3), 2.97 (s, 3), 3.16 (s, 3), 3.74-3.87 (m, 4), 4.26 (hept, 1, J=6.8), 5.09 (s, 2), 6.69 (dt, 1, J=10.5, 2.3), 6.74 (ddd, 1, J=10.1, 2.3, 1.5), 6.84 (m, 1), 7.12 (d, 2, J=8.7), 7.45 (d, 2, J=8.7); MS (APCI+) m/z 445 $(M+H)^+$.

Example 73

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1-azetidinecarboxamide

The product from Example 30H and azetidine were processed as described in Example 30I to provide the title compound as a bright yellow oil. $^1$H NMR (400 MHz, $CD_3OD$) δ 1.89-2.04 (m, 6), 2.97 (s, 3), 3.12 (s, 3), 3.57 (t, 4, J=7.7), 3.72-3.87 (m, 4), 5.13 (s, 2), 6.70 (dt, 1, J=10.5, 2.3), 6.74 (ddd, 1, J=10.1, 2.3, 1.5), 6.85 (m, 1), 7.28 (d, 2, J=8.4), 7.49 (d, 2, J=8.4); MS (APCI+) m/z 429 $(M+H)^+$.

Example 74

N'-cyclobutyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea

The product from Example 30H and cyclobutylamine were processed as described in Example 30I to provide the title compound as an off white solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.62 (m, 2), 1.79-1.90 (m, 2), 1.92-2.02 (m, 4), 2.21 (m, 2), 2.98 (s, 3), 3.21 (s, 3), 3.74-3.87 (m, 4), 4.19 (quint, 1, J=8.0), 5.13 (s, 2), 6.72 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.29 (d, 2, J=8.5), 7.53 (d, 2, J=8.7); MS (APCI+) m/z 443 $(M+H)^+$.

Example 75

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-(tetrahydro-2-furanylmethyl)urea

The product from Example 30H and tetrahydro-2-furanylmethylamine were processed as described in Example 30I to provide the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.55 (m, 1), 1.86 (m, 2), 1.89-2.02 (m, 5), 2.97 (s, 3), 3.14 (m, 1), 3.23 (s, 3), 3.26 (m, 1), 3.67 (m, 1), 3.70-3.88 (m, 6), 5.14 (s, 2), 6.71 (dt, 1, J=10.5, 2.1), 6.75 (ddd, 1, J=10.1, 2.1, 1.5), 6.86 (m, 1), 7.32 (d, 2, J=8.5), 7.54 (d, 2, J= 8.5); MS (APCI+) m/z 473 $(M+H)^+$.

Example 76

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-methoxyethyl)-N-methylurea

The product from Example 30H and 2-methoxyethylamine were processed as described in Example 30I to provide the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.91-2.01 (m, 4), 2.97 (s, 3), 3.23 (s, 3), 3.29 (s, 3), 3.29 (t, 2, J=5.5), 3.39 (t, 2, J=5.5), 3.74-3.87 (m, 4), 5.14 (s, 2), 6.71 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.31 (d, 2, J=8.6), 7.53 (d, 2, J=8.6); MS (APCI+) m/z 447 $(M+H)^+$.

Example 77

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-propylurea

The product from Example 30H and propylamine were processed as described in Example 30I to provide the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.85 (t, 3, J=7.5); 1.46 (m, 2); 1.90-2.02 (m, 4), 2.98 (s, 3), 3.07 (t, 2, J=7.1); 3.22 (s, 3), 3.75-3.87 (m, 4), 5.13 (s, 2), 6.71 (dt, 1, J= 10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.30 (d, 2, J=8.6), 7.53 (d, 2, J=8.6); MS (APCI+) m/z 431 $(M+H)^+$.

Example 78

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-hydroxy-1-methylethyl)-N-methylurea

The product from Example 30H and 2-amino-1-propanol were processed as described in Example 30I to provide the title compound as an off white oily solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.08 (d, 2, J=6.8), 1.91-2.01 (m, 4), 2.97 (s, 3), 3.24 (s, 3), 3.43 (dd, 2, J=5.2, 1.6), 3.74-3.89 (m, 5), 5.13 (s, 2), 6.71 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.32 (d, 2, J=8.5), 7.53 (d, 2, J=8.5); MS (APCI+) m/z 447 $(M+H)^+$.

Example 79

N'-(1-ethylpropyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea

The product from Example 30H and 1-ethylpropylamine were processed as described in Example 30I to provide the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.86 (t, 6, J=7.4), 1.31 (m, 2), 1.46 (m, 2), 1.90-2.02 (m, 4), 2.98 (s, 3), 3.23 (s, 3), 3.54 (m, 1), 3.74-3.87 (m, 4), 5.14 (s, 2), 6.71 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.0, 2.3, 1.5), 6.87 (m, 1), 7.31 (d, 2, J=8.5), 7.54 (d, 2, J=8.5); MS (APCI+) m/z 459 $(M+H)^+$.

Example 80

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-(2,2,2-trifluoroethyl)urea

The product from Example 30H and 2,2,2-trifluoroethylamine were processed as described in Example 30I to provide the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.91-2.01 (m, 4), 2.98 (s, 3), 3.25 (s, 3), 3.75-3.87 (m, 6), 5.14 (s, 2), 6.71 (dt, 1, J=10.5, 2.3), 6.76 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.31 (d, 2, J=8.6), 7.55 (d, 2, J=8.6).

Example 81

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-neopentylurea

The product from Example 30H and 2,2-dimethyl-1-propylamine were processed as described in Example 30I to provide the title compound as a light yellow solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.81 (s, 9), 1.90-2.01 (m, 4), 2.95 (s, 2), 2.98 (s, 3), 3.24 (s, 3), 3.74-3.87 (m, 4), 5.15 (s, 2), 6.71 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.87 (m, 1), 7.33 (d, 2, J=8.5), 7.56 (d, 2, J=8.5); MS (APCI+) m/z 459 $(M+H)^+$.

Example 82

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-isobutyl-N-methylurea

The product from Example 30H and 2-methyl-1-propylamine were processed as described in Example 30I to provide the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.84 (d, 6, J=6.7), 1.71 (hept, 1, J=6.8), 1.91-2.01 (m, 4), 2.93 (d, 2, J=7.0), 2.98 (s, 3), 3.23 (s, 3), 3.74-3.86 (m, 4), 5.13 (s, 2), 6.71 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.31 (d, 2, J=8.6), 7.54 (d, 2, J=8.6); MS (APCI+) m/z 445 $(M+H)^+$.

Example 83

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-(2-methylbutyl)urea

The product from Example 30H and 2-methylbutylamine were processed as described in Example 30I to provide the title compound as a light yellow solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.82 (d, 3, J=6.7), 0.88 (t, 3, J= 7.4), 1.07 (m, 1), 1.35 (m, 1), 1.50 (m, 1), 1.90-2.01 (m, 4), 2.91 (dd, 1, J=13.3, 7.3), 2.98 (s, 3), 3.06 (dd, 1, J=13.3, 6.3), 3.23 (s, 3), 3.75-3.86 (m, 4), 5.14 (s, 2), 6.71 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.30 (d, 2, J=8.3), 7.54 (d, 2, J=8.3); MS (APCI+) m/z 459 $(M+H)^+$.

Example 84

N'-(2-ethylhexyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea

The product from Example 30H and 2-ethylhexylamine were processed as described in Example 30I to provide the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.86 (t, 3, J=7.5), 0.90 (m, 3), 1.16-1.36 (m, 8), 1.40 (m, 1), 1.91-2.02 (m, 4), 2.98 (s, 3), 3.06 (m, 2), 3.23 (s, 3), 3.74-3.87 (m, 4), 5.14 (s, 2), 6.71 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.30 (d, 2, J=8.6), 7.54 (d, 2, J=8.6); MS (APCI+) m/z 501 $(M+H)^+$.

Example 85

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-(2-propynyl)urea

The product from Example 30H and 2-propynylamine were processed as described in Example 30I to provide the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.91-2.01 (m, 4), 2.47 (t, 1, J=2.5), 2.98 (s, 3), 3.24 (s, 3), 3.75-3.86 (m, 4), 3.87 (d, 2, J=2.5), 5.14 (s, 2), 6.71 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.30 (d, 2, J=8.6), 7.53 (d, 2, J=8.6); MS (APCI+) m/z 427 $(M+H)^+$.

Example 86

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-hydroxybutyl)-N-methylurea

The product from Example 30H and 1-amino-2-butanol were processed as described in Example 30I to provide the title compound as a light yellow solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.93 (t, 3, J=7.5), 1.36 (m, 1), 1.44 (m, 1), 1.90-2.02 (m, 4), 2.98 (s, 3), 3.00 (dd, 1, J=13.8, 7.5), 3.24 (s, 3), 3.28 (dd, 2, J=13.8, 3.9), 3.49 (m, 1), 3.75-3.87 (m, 4), 5.13 (s, 2), 6.71 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.33 (d, 2, J=8.6), 7.54 (d, 2, J=8.6); MS (APCI+) m/z 461 $(M+H)^+$.

Example 87

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(3-hydroxy-2,2-dimethylpropyl)-N-methylurea

The product from Example 30H and 3-amino-2,2-dimethyl-1-propanol were processed as described in Example 30I to provide the title compound as a white solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.80 (s, 6), 1.91-2.02 (m, 4), 2.98 (s, 3), 3.02 (s, 2), 3.18 (s, 2), 3.24 (s, 3), 3.74-3.87 (m, 4), 5.14 (s, 2), 6.72 (dt, 1, J=10.5, 2.3), 6.76 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.32 (d, 2, J=8.6), 7.55 (d, 2, J=8.6); MS (APCI+) m/z 475 $(M+H)^+$.

Example 88

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-[2-(2-hydroxyethoxy)ethyl]-N-methylurea

The product from Example 30H and 2-(2-aminoethoxy)ethanol were processed as described in Example 30I to provide the title compound as a colorless oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.91-2.02 (m, 4), 2.98 (s, 3), 3.24 (s, 3), 3.32 (m, 2), 3.49 (m, 4), 3.61 (m, 2), 3.74-3.86 (m, 4), 5.13 (s, 2), 6.71 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.31 (d, 2, J=8.6), 7.53 (d, 2, J=8.6); MS (APCI+) m/z 477 $(M+H)^+$.

Example 89

N'-allyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea

The product from Example 30H and allylamine were processed as described in Example 30I to provide the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.91-2.01 (m, 4), 2.97 (s, 3), 3.24 (s, 3), 3.73 (dt, 2, J= 5.3, 1.7), 3.75-3.86 (m, 4), 5.02 (dq, 1, J=10.3, 1.6), 5.09 (dq, 1, J=17.2, 1.7), 5.13 (s, 2), 5.81 (m, 1), 6.71 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.31 (d, 2, J=8.6), 7.53 (d, 2, J=8.6); MS (APCI+) m/z 429 $(M+H)^+$.

Example 90

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-methoxy-1-methylethyl)-N-methylurea

The product from Example 30H and 2-methoxy-1-methylethylamine were processed as described in Example 30I to provide the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.07 (d, 3, J=6.8), 1.91-2.01 (m, 4), 2.97 (s, 3), 3.23 (s, 3), 3.28 (dd, 1, J=6.4, 5.3), 3.28 (s, 3), 3.31 (m, 1), 3.74-3.87 (m, 4), 3.96 (m, 1), 5.14 (s, 2), 6.71 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.87 (m, 1), 7.31 (d, 2, J=8.6), 7.53 (d, 2, J=8.6); MS (APCI+) m/z 461 $(M+H)^+$.

Example 91

N'-(cyanomethyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea

The product from Example 30H and aminoacetonitrile were processed as described in Example 30I to provide the title compound as an off white solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.91-2.01 (m, 4), 2.98 (s, 3), 3.25 (s, 3), 3.74-3.87 (m, 4), 4.02 (s, 2), 5.14 (s, 2), 6.71 (dt, 1, J=10.5, 2.3), 6.76 (ddd, 1, J=10.1, 2.3, 1.5), 6.87 (m, 1), 7.32 (d, 2, J=8.5), 7.55 (d, 2, J=8.5).

Example 92

N'-cyclopropyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea

The product from Example 30H and cyclopropylamine were processed as described in Example 30I to provide the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.40 (m, 2), 0.68 (m, 2), 1.90-2.01 (m, 4), 2.61 (m, 1), 2.97 (s, 3), 3.21 (s, 3), 3.73-3.86 (m, 4), 5.12 (s, 2), 6.71 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.26 (d, 2, J=8.6), 7.50 (d, 2, J=8.6); MS (APCI+) m/z 429 $(M+H)^+$.

Example 93

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-isopropyl-N-methyl-N'-propylurea

The product from Example 30H and N-isopropyl-N-propylamine were processed as described in Example 30I to provide the title compound as an oily colorless solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.79 (t, 3, J= 7.4), 0.95 (d, 6, J= 6.8), 1.47 (m, 2), 1.90-2.00 (m, 4), 2.84 (m, 2), 2.97 (s, 3), 3.13 (s, 3), 3.74-3.86 (m, 4), 4.05 (hept, 1, J=6.8), 5.10 (s, 2), 6.68 (dt, 1, J=10.5, 2.3), 6.74 (ddd, 1, J=10.1, 2.3, 1.5), 6.85 (m, 1), 7.14 (d, 2, J=8.7), 7.46 (d, 2, J=8.7); MS (APCI+) m/z 473 $(M+H)^+$.

Example 94

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-[(1R)-1-(hydroxymethyl)propyl]-N-methylurea

The product from Example 30H and (2R)-2-amino-1-butanol were processed as described in Example 30I to provide the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.89 (t, 3, J=7.5), 1.36 (m, 1), 1.55 (m, 1), 1.90-2.02 (m, 4), 2.97 (s, 3), 3.24 (s, 3), 3.47 (m, 2), 3.65 (m, 1), 3.74-3.87 (m, 4), 5.13 (s, 2), 6.71 (dt, 1, J= 10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.33 (d, 2, J=8.5), 7.54 (d, 2, J=8.5); MS (APCI+) m/z 461 $(M+H)^+$.

Example 95

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-(2-methyl-2-propenyl)urea

The product from Example 30H and 2-methyl-2-propenylamine were processed as described in Example 30I to provide the title compound as a colorless oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.68 (s, 3), 1.91-2.01 (m, 4), 2.97 (s, 3), 3.24 (s, 3), 3.67 (s, 2), 3.74-3.86 (m, 4), 4.75 (m, 2), 5.14 (s, 2), 6.71 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.33 (d, 2, J=8.6), 7.54 (d, 2, J=8.6); MS (APCI+) m/z 443 $(M+H)^+$.

Example 96

(2R)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-2-(hydroxymethyl)-N-methyl-1-pyrrolidinecarboxamide

The product from Example 30H and (2R)-pyrrolidinylmethanol were processed as described in Example 30I to provide the title compound as a white solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.55-1.74 (m, 3), 1.89-2.01 (m, 5), 2.58 (m, 1), 2.97 (s, 3), 3.08 (m, 1), 3.20 (s, 3), 3.62 (dd, 1, J=10.9, 5.7), 3.67 (dd, 1, J=10.9, 4.1), 3.73-3.86 (m, 4), 4.01 (m, 1), 5.09 (s, 2), 6.69 (dt, 1, J=10.5, 2.3), 6.74 (ddd, 1, J=10.1, 2.3, 1.5), 6.84 (m, 1), 7.22 (d, 2, J=8.6), 7.45 (d, 2, J=8.6); MS (APCI+) m/z 473 $(M+H)^+$.

Example 97

N'-(2-fluoroethyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea

The product from Example 30H and 2-fluoroethylamine were processed as described in Example 30I to provide the title compound as a yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.91-2.01 (m, 4), 2.97 (s, 3), 3.24 (s, 3), 3.40 (dt, 2, J=24.7, 5.2), 3.74-3.87 (m, 4), 4.38 (dt, 2, J=47.5, 5.2), 5.13 (s, 2), 6.71 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.31 (d, 2, J=8.6), 7.53 (d, 2, J=8.6); MS (APCI+) m/z 435 $(M+H)^+$.

Example 98

N'-ethyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea

The product from Example 30H and ethylamine were processed as described in Example 30I to provide the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.05 (t, 3, J=7.2), 1.91-2.01 (m, 4), 2.98 (s, 3), 3.15 (q, 2, J=7.2), 3.22 (s, 3), 3.74-3.87 (m, 4), 5.13 (s, 2), 6.71 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.29 (d, 2, J=8.6), 7.52 (d, 2, J=8.6); MS (APCI+) m/z 417 $(M+H)^+$.

Example 99

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-hydroxypropyl)-N-methylurea

The product from Example 30H and 1-amino-2-propanol were processed as described in Example 30I to provide the title compound as a yellowish solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.03 (d, 3, J=6.3), 1.90-2.01 (m, 4), 2.98 (s, 3), 3.01 (dd, 1, J=13.7, 7.2), 3.20 (dd, 1, J=13.7, 4.3), 3.24 (s, 3), 3.74-3.87 (m, 5), 5.13 (s, 2), 6.71 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.33 (d, 2, J=8.5), 7.54 (d, 2, J=8.5); MS (APCI+) m/z 447 $(M+H)^+$.

Example 100

N'-(cyclopropylmethyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea

The product from Example 30H and cyclopropylmethylamine were processed as described in Example 30I to provide the title compound as a colorless oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.14 (m, 2), 0.41 (m, 2), 0.95 (m, 1), 1.90-2.01 (m, 4), 2.98 (s, 3), 2.99 (m, 2), 3.23 (s, 3), 3.74-3.87 (m, 4), 5.13 (s, 2), 6.71 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.87 (m, 1), 7.31 (d, 2, J=8.6), 7.53 (d, 2, J=8.6); MS (APCI+) m/z 443 $(M+H)^+$.

Example 101

N'-(2-ethylbutyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea

The product from Example 30H and 2-ethylbutylamine were processed as described in Example 30I to provide the title compound as an off white solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.86 (t, 6, J=7.4), 1.25 (m, 4), 1.34 (m, 1), 1.91-2.02 (m, 4), 2.98 (s, 3), 3.06 (d, 2, J=6.5), 3.23 (s, 3), 3.74-3.87 (m, 4), 5.14 (s, 2), 6.71 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.87 (m, 1), 7.30 (d, 2, J=8.5), 7.54 (d, 2, J=8.6); MS (APCI+) m/z 473 $(M+H)^+$.

Example 102

(2S)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-2-(hydroxymethyl)-N-methyl-1-pyrrolidinecarboxamide

The product from Example 30H and (2S)-pyrrolidinylmethanol were processed as described in Example 30I to provide the title compound as a white solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.54-1.74 (m, 3), 1.87-2.01 (m, 5), 2.58 (m, 1), 2.97 (s, 3), 3.08 (m, 1), 3.20 (s, 3), 3.62 (dd, 1, J=10.9, 5.7), 3.67 (dd, 1, J=10.9, 4.1), 3.73-3.86 (m, 4), 4.01 (m, 1), 5.09 (s, 2), 6.69 (dt, 1, J=10.5, 2.2), 6.74 (ddd, 1, J=10.1, 2.2, 1.3), 6.84 (m, 1), 7.22 (d, 2, J=8.4), 7.45 (d, 2, J=8.4); MS (APCI+) m/z 473 $(M+H)^+$.

Example 103

N'-cyclopentyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea

The product from Example 30H and cyclopentylamine were processed as described in Example 30I to provide the title compound as an off white solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.32 (m, 2), 1.49-1.65 (m, 4), 1.84-2.02 (m, 6), 2.97 (s, 3), 3.22 (s, 3), 3.74-3.86 (m, 4), 4.01 (quint, 1, J=7.1), 5.13 (s, 2), 6.71 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.29 (d, 2, J=8.6), 7.52 (d, 2, J=8.6); MS (APCI+) m/z 457 $(M+H)^+$.

Example 104

N'-(1,2-dimethylpropyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea

The product from Example 30H and 1,2-dimethylpropylamine were processed as described in Example 30I to provide the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.81 (d, 3, J=6.8), 0.84 (d, 3, J=6.8), 1.01 (d, 3, J=6.8), 1.60 (hept, 1, J=6.8), 1.90-2.02 (m, 4), 2.98 (s, 3), 3.23 (s, 3), 3.61 (m, 1), 3.75-3.86 (m, 4), 5.14 (s, 2), 6.71 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.6), 6.85 (m, 1), 7.31 (d, 2, J=8.5), 7.55 (d, 2, J=8.5); MS (APCI+) m/z 459 $(M+H)^+$.

Example 105

N'-sec-butyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea

The product from Example 30H and sec-butylamine were processed as described in Example 30I to provide the title compound as a colorless oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.86 (t, 3, J=7.4), 1.05 (d, 3, J=6.6), 1.39 (m, 2), 1.90-2.01 (m, 4), 2.98 (s, 3), 3.23 (s, 3), 3.69 (m, 1), 3.74-3.87 (m, 4), 5.13 (s, 2), 6.71 (dt, 1, J=10.5, 2.2), 6.75 (ddd, 1, J=10.1, 2.2, 1.5), 6.87 (m, 1), 7.30 (d, 2, J=8.5), 7.53 (d, 2, J=8.5); MS (APCI+) m/z 445 $(M+H)^+$.

Example 106

N'-[bicyclo[2.2.1]hept-2-yl]-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea

The product from Example 30H and bicyclo[2.2.1]hept-2-ylamine were processed as described in Example 30I to provide the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.10 (m, 3), 1.19 (m, 2), 1.40-1.52 (m, 2), 1.67 (ddd, 1, J=13.0, 7.9, 2.3), 1.90-2.01 (m, 4), 2.13 (br d, 1, J=4.4), 2.17 (m, 1), 2.97 (s, 3), 3.22 (s, 3), 3.52 (br dd, 1, J=8.1, 3.6), 3.75-3.87 (m, 4), 5.14 (s, 2), 6.71 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.87 (m, 1), 7.29 (d, 2, J=8.6), 7.53 (d, 2, J=8.6); MS (APCI+) m/z 483 $(M+H)^+$.

Example 107

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-[2-(4-hydroxyphenyl)ethyl]-N-methylurea

The product from Example 30H and 4-(2-aminoethyl)phenol were processed as described in Example 30I to provide the title compound as a yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.91-2.02 (m, 4), 2.64 (t, 2, J=7.1), 2.98 (s, 3), 3.20 (s, 3), 3.20 (t, 2, J=7.1), 3.74-3.87 (m, 4), 5.12 (s, 2), 6.68 (d, 2, J=8.6), 6.72 (dt, 1, J=10.5, 2.3), 6.76 (ddd, 1, J=10.1, 2.3, 1.5), 6.87 (m, 1), 6.94 (d, 2, J=8.6), 7.18 (d, 2, J=8.6), 7.47 (d, 2, J=8.6); MS (APCI+) m/z 509 $(M+H)^+$.

Example 108

N'-(2-cyanoethyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea

The product from Example 30H and 3-aminopropanenitrile were processed as described in Example 30I to provide the title compound as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.91-2.02 (m, 4), 2.62 (t, 2, J=6.6), 2.98 (s, 3), 3.24 (s, 3), 3.36 (t, 2, J=6.6), 3.74-3.87 (m, 4), 5.14 (s, 2), 6.71 (dt, 1, J=10.5, 2.3), 6.75 (dt, 1, J=10.1, 1.7), 6.86 (m, 1), 7.33 (d, 2, J=8.3), 7.54 (d, 2, J=8.3).

Example 109

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-hydroxyethyl)-N-methylurea

The product from Example 30H and 2-aminoethanol were processed as described in Example 30I to provide the title compound as an oily white solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.90-2.02 (m, 4), 2.98 (s, 3), 3.24 (s, 3), 3.24 (t, 2, J= 5.7), 3.54 (t, 2, J= 5.7), 3.74-3.87 (m, 4), 5.13 (s, 2), 6.71 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.32 (d, 2, J=8.6), 7.53 (d, 2, J=8.6); MS (APCI+) m/z 433 $(M+H)^+$.

Example 110

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-[1-(hydroxymethyl)cyclopentyl]-N-methylurea

The product from Example 30H and (1-aminocyclopentyl)methanol were processed as described in Example 30I to provide the title compound as a tan solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.59 (m, 2), 1.66 (m, 4), 1.75 (m, 2), 1.91-2.01 (m, 4), 2.97 (s, 3), 3.21 (s, 3), 3.38 (s, 2), 3.74-3.87 (m, 4), 5.14 (s, 2), 6.71 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.34 (d, 2, J=8.6), 7.54 (d, 2, J=8.6); MS (APCI+) m/z 487 $(M+H)^+$.

Example 111

N'-(2,2-dimethylcyclopentyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea

The product from Example 30H and 2,2-dimethylcyclopentylamine were processed as described in Example 30I to provide the title compound as a tan solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.65 (s, 3), 0.98 (s, 3), 1.31 (m, 1), 1.43 (m, 2), 1.57 (m, 2), 1.90-2.03 (m, 5), 2.98 (s, 3), 3.24 (s, 3), 3.74-3.87 (m, 5), 5.15 (s, 2), 6.70 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.87 (m, 1), 7.33 (d, 2, J=8.5), 7.56 (d, 2, J=8.6); MS (APCI+) m/z 485 $(M+H)^+$.

Example 112

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-isopropyl-N-methylurea

The product from Example 30H and isopropylamine were processed as described in Example 30I to provide the title compound as a colorless oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.08 (d, 6, J=6.6), 1.90-2.01 (m, 4), 2.98 (s, 3), 3.22 (s, 3), 3.74-3.85 (m, 4), 3.89 (hept, 1, 6.6), 5.13 (s, 2), 6.71 (dt, 1, J=10.5, 2.9), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.29 (d, 2, J=8.6), 7.53 (d, 2, J=8.6); MS (APCI+) m/z 431 $(M+H)^+$.

Example 113

N,N-diethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea

The product from Example 30H and diethylamine were processed as described in Example 30I to provide the title compound as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, 6, J=7.1), 1.90-2.01 (m, 4), 2.97 (s, 3), 3.12 (q, 4, J=7.1), 3.15 (s, 3), 3.75-3.87 (m, 4), 5.00 (s, 2), 6.60 (dt, 1, J=10.3, 2.3), 6.70 (ddd, 1, J=9.9, 2.0, 1.6), 6.80 (m, 1), 7.09 (d, 2, J=8.4), 7.37 (d, 2, J=8.4); MS (APCI+) m/z 445 $(M+H)^+$.

(292753) Example 114

N-ethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-(2-methoxyethyl)-N'-methylurea

The product from Example 30H and N-ethyl-N-(2-methoxyethyl)amine were processed as described in Example 30I to provide the title compound as a light yellow solid. $^1$H NMR (400 MHz, $CD_3OD$) δ 0.93 (t, 3, J= 7.1), 1.88-2.02 (m, 4), 2.97 (s, 3), 3.12 (q, 2, J=7.1), 3.14 (s, 3), 3.28 (s, 3), 3.34 (m, 4), 3.73-3.87 (m, 4), 5.09 (s, 2), 6.69 (dt, 1, J=10.5, 2.3), 6.74 (ddd, 1, J=10.1, 2.3, 1.5), 6.85 (m, 1), 7.17 (d, 2, J=8.7), 7.45 (d, 2, J=8.7); MS (APCI+) m/z 475 $(M+H)^+$.

Example 115

N-butyl-N-(cyanomethyl)-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea

The product from Example 30H and (butylamino)acetonitrile were processed as described in Example 30I to provide the title compound as a colorless oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.78 (t, 3, J=7.4), 1.07 (m, 2), 1.24 (m, 2), 1.90-2.00 (m, 4), 2.98 (s, 3), 3.00 (m, 2), 3.19 (s, 3), 3.74-3.86 (m, 4), 4.13 (s, 2), 5.12 (s, 2), 6.70 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.22 (d, 2, J=8.5), 7.51 (d, 2, J=8.5); MS (APCI+) m/z 501 $(M+H_2O)^+$.

Example 116

N$^1$-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N$^1$-methyl-1,3-piperidinedicarboxamide

The product from Example 30H and 3-piperidinecarboxamide were processed as described in Example 30I to provide the title compound as a colorless oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.30 (m, 1), 1.46-1.62 (m, 2), 1.85 (m, 1), 1.90-2.01 (m, 4), 2.28 (m, 1), 2.63 (ddd, 1, J=13.9, 11.0, 2.2), 2.83 (dd, 1, J=13.2, 10.5), 2.97 (s, 3), 3.19 (s, 3), 3.60 (m, 1), 3.73-3.87 (m, 5), 5.09 (s, 2), 6.70 (dt, 1, J=10.5, 2.2), 6.75 (dt, 1, J=10.1, 1.8), 6.85 (m, 1), 7.16 (d, 2, J=8.4), 7.47 (d, 2, J=8.4); MS (APCI+) m/z 500 $(M+H)^+$.

Example 117

N-butyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethylurea

The product from Example 30H and N-butyl-N-methylamine were processed as described in Example 30I to provide the title compound as a colorless oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.89 (t, 3, J=7.4), 1.23 (m, 2), 1.41 (m, 2), 1.86-1.98 (m, 4), 2.62 (s, 3), 2.97 (s, 3), 3.13 (m, 2), 3.16 (s, 3), 3.74-3.86 (m, 4), 5.09 (s, 2), 6.70 (dt, 1, J=10.5, 2.3), 6.74 (ddd, 1, J= 10.1, 2.3, 1.5), 6.85 (m, 1), 7.11 (d, 2, J=8.5), 7.45 (d, 2, J=8.5); MS (APCI+) m/z 459 $(M+H)^+$.

Example 118

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-isopropyl-N'-(2-methoxyethyl)-N-methylurea

The product from Example 30H and N-isopropyl-N-(2-methoxyethyl)amine were processed as described in Example 30I to provide the title compound as a colorless oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.90 (d, 6, J=6.7), 1.90-2.00 (m, 4), 2.97 (s, 3), 3.13 (s, 3), 3.18 (t, 2, J=6.1), 3.32 (s, 3), 3.41 (t, 2, J=6.1), 3.74-3.86 (m, 4), 3.97 (hept, 1, J=6.7), 5.10 (s, 2), 6.68 (dt, 1, J=10.5, 2.3), 6.74 (ddd, 1, J=10.1, 2.3, 1.5), 6.85 (m, 1), 7.18 (d, 2, J=8.5), 7.45 (d, 2, J=8.5); MS (APCI+) m/z 489 $(M+H)^+$.

Example 119

N,N-diethyl-N'-(4-{[3-fluoro-5-(4-hydroxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea

The product from Example 1D (248 mg, 1.05 mmol) in 2 mL of DMF at 0 °C was treated with sodium hydride (76 mg, 3.17 mmol). The cooling bath was removed and the reaction mixture was treated with the product from Example 30D (214 mg, 1.0 mmol) in 1 mL of DMF. After 3 hours at ambient temperature, the mixture was warmed to 65 °C for 4 days and then 90 °C for 16 hours. The mixture was partitioned between diethyl ether and water and the organic phase was washed with water and concentrated in vacuo. The crude material was purified by column chromatography (98:2 $CHCl_3$:MeOH) to provide 176 mg (41%) of the title compound as a clear oil. $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.95 (t, 6, J=7.0), 1.65 (d, 2, J=12.8), 2.10 (dt, 2, J=13.2, 5.6), 3.11 (q, 4, J=7.0), 3.15 (s, 3), 3.90 (m, 4), 5.00 (s, 2), 6.58 (dt, 1, J=10.0, 2.0), 6.82 (br d, 1, J=10.0), 6.90 (br s, 1), 7.10 (d, 2, J=8.4), 7.35 (d, 2, J= 8.4); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 19.9, 38.6, 39.6, 42.0, 63.7, 69.9, 70.6, 100.8 (d), 104.4 (d), 107.5 (d), 123.6, 128.7, 132.2, 147.2, 151.9 (d), 159.9 (d), 162.0 (d), 164.8; IR 3393, 2962, 2870, 1613, 1434 $cm^{-1}$; HRMS calcd for $C_{24}H_{32}FN_2O_4$ 431.2346; found: 431.2352.

Example 120

N-(4-{[3-fluoro-5-(4-hydroxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide

The product from Example 15C, the product from Example 30D, and sodium hydride were processed as described in Example 119. The residue was purified by column chromatography (98:2 $CHCl_3$:MeOH) to provide the title compound as a colorless oil. $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.25 (d, 3, J=6.0), 1.3-1.4 (m, 1), 1.56-1.7 (m, 3), 1.95-2.2 (m, 5), 2.55-2.67 (m, 1), 3.02-3.25 (m, 2 ), 3.23 (s, 3), 3.84-4.02 (m, 4), 5.0 (s, 2), 6.59(dt, 1, J=10.6, 2.2), 6.86(dt, 1, J=12.0, 2.2), 6.94 (m,1), 7.14 (d, 2, J=9), 7.39 (d, 2, J=9); MS (APCI+) m/z 443 $(M+H)^+$.

Example 121

N-(4-{[3-fluoro-5-(4-hydroxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N',N'-trimethylurea

Example 121A

N-[4-(hydroxymethyl)phenyl]-N,N',N'-trimethylurea

The title compound was prepared using dimethylamine and the procedure(s) described in Example 1A through Example 1D.

Example 121B

N-(4-{[3-fluoro-5-(4-hydroxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N',N'-trimethylurea

The product from Example 121A and the product from Example 30D were processed as described in Example 119 to provide the title compound. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.55-1.65 (m,2), 2.02-2.2 (m, 2), 2.65(s, 6), 3.23 (s, 3), 3.82-3.98 (m, 4), 5.0 (s, 2), 6.60(dt, 1, J=10.3, 2.3), 6.83(ddd, 1, J=10.3, 2.3, 1.6), 6.94 (m,1), 7.0 (d, 2, J=8.5), 7.3 (d, 2, J=8.5); MS (APCI+) m/z 403 $(M+H)^+$.

Example 122

N-[4-({3-fluoro-5-[4-(2-propynyloxy)tetrahydro-2H-pyran-4-yl]phenoxy}methyl)phenyl]-N,N',N'-trimethylurea

The product from Example 121B, propargyl bromide, and sodium hydride were processed as described in Example 119 to provide the title compound. $^1$H NMR (300 MHz, $CD_3OD$) δ 1.84-1.94 (m, 4), 2.6 (s, 6), 2.69 (t, 1, J=2.5), 3.08 (s, 3), 3.66 (d, 2, J=2.5), 3.68 (m, 2), 3.82 (m, 2) 5.0 (s, 2), 6.71 (dt, 1, J=10.5, 2.2), 6.77 (ddd, 1, J=10.0, 2.3, 1.5), 6.88 (m, 1), 7.10 (d, 1, J=8.6), 7.45 (d, 1, J=8.6); MS (DCI/$NH_3$) m/z 441 $(M+H)^+$.

Example 123

N,N-diethyl-N'-(4-{[3-(4-ethyltetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea

Example 123A

4-[3-(benzyloxy)phenyl]tetrahydro-2H-pyran-4-carbaldehyde

The title compound was prepared according to the procedure described in EP 0 462 830 A2.

Example 123B

4-[3-(benzyloxy)phenyl]-4-vinyltetrahydro-2H-pyran

Methyltriphenylphosphonium bromide (0.15 g, 0.41 mmol) in 8 mL of anhydrous THF:$Et_2O$ (3:1) was slowly treated with a solution of n-butyllithium in hexane (2.5 M, 0.17 mL, 0.41 mmol) via syringe. After 2 hours at ambient temperature, the reaction mixture was treated with the product from Example 123A (0.11 g, 0.37 mmol) in 3 mL of diethyl ether. The reaction mixture was stirred overnight and the resultant precipitate was filtered, washed with diethyl ether, and chromatographed on silica gel (90:10 hexanes:acetone) to provide 0.025 grams (25%) of the title compound as a glassy solid. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.98 (dt, 2, J=12, 7.5), 2.1-2.2 (m, 2), 3.7-3.8 (m, 4), 4.95 (dd, 1, J=18.0, 1.0), 5.05 (s, 2), 5.15 (dd, 1, J=10.5,1), 5.82 (dd, 1, J=18,10.5), 6.82 (dd, 1, J=7.5, 2), 6.92 (m, 2), 7.25 (s,1), 7.3-7.49 (m, 5).

Example 123C

3-(4-ethyltetrahydro-2H-pyran-4-yl)phenol

The product from Example 123B (0.048 g, 0.163 mmol) in EtOH (2 mL) was treated with 10% Pd/C (0.03 g) under an atmosphere of hydrogen overnight. The mixture was then filtered through Celite and a 0.2 micron filter and evaporated in vacuo to provide 0.025 grams (75%) of the title compound as a white solid. $^1$H NMR (300 MHz, $CDCl_3$) δ 0.56 (t, 3, J=7.5), 1.62 (q, 2, J=7.5), 1.7-1.82 (m, 2), 2.02-2.18 (m, 2), 3.5-3.62 (dt, 2, J=8, 3), 3.72-3.82

(m, 2), 4.05 (q, 2, J=9), 6.65 (dd, 1, J=8, 2), 6.78 (m, 1), 6.82 (d, 1, J=8), 7.2 (t, 1, J=8); MS (DCI/$NH_3$) m/z 224 $(M+NH_4)^+$.

Example 123D

N-[4-(bromomethyl)phenyl]-N',N'-diethyl-N-methylurea

The product from Example 1D (1.6 g, 6.8 mmol) in 10 mL of $CCl_4$ was treated with pyridine (0.27 mL, 3.4 mmol) followed by phosphorous tribromide (1.3 mL, 14.1 mmol) at 0 °C. The reaction mixture was stirred for 1 hour at 0 °C and then allowed to warm to ambient temperature and stirred overnight. The mixture was poured into iced water and extracted with $CH_2Cl_2$ (50 mL, 2X). The combined organic phases were combined, washed with brine, water, dried over $MgSO_4$, filtered, and concentrated in vacuo to provide 1.56 grams (77%) of the title compound as a semisolid. $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 6, J=7), 3.3.1-3.15 (m, 7), 4.49 (s, 2), 7.04 (d, 2, J=9), 7.44 (d, 2, J=9); MS (APCI+) m/z 299, 301 $(M+H)^+$.

Example 123E

N,N-diethyl-N'-(4-{[3-(4-ethyltetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea

The product from Example 123C (0.021 g, 0.11 mmol) in 1mL of DMF was treated with solid sodium hydride (0.005 g, 0.2 mmol) at ambient temperature. After stirring for 30 minutes, the reaction mixture was treated with the product from Example 123D (0.036 g, 0.12 mmol) in 0.5 mL of DMF. The mixture was stirred overnight. The mixture was quenched with water and saturated aqueous $NH_4Cl$ (3 ml) and extracted with diethyl ether and ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to provide an oily residue (0.109 g), which was chromatographed on silica gel (80:20 hexanes:acetone) to provide 0.018 grams (36%) of the title compound as a glassy solid. $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.56 (t, 3, J=7.5), 0.9-1.01 (m, 6),1.58-1.66 (dd, 2, J=7.5), 1.7-1.82 (ddd, 2, J=10, 3, 3), 2.04-2.18 (dt, 2, J=7.5, 3), 3.05-3.25 (m, 7), 3.5-3.6 (dt, 2, J=10, 3), 3.72-3.82 (m, 2), 5.02 (s, 2), 6.82 (dd, 1, J=8, 2), 6.89 (m, 2), 7.1 (d, 2, J=8), 7.25 (m,1), 7.4 (d, 2, J=8); MS (APCI+) m/z 425 $(M+H)^+$.

Example 124

ethyl 4-[3-({4-[[(diethylamino)carbonyl](methyl)amino]benzyl}oxy)phenyl]tetrahydro-2H-pyran-4-carboxylate

Example 124A

ethyl 4-[3-(benzyloxy)phenyl]tetrahydro-2H-pyran-4-carboxylate

The title compound was prepared according to the procedure described in EP 0 462 830 A2.

Example 124B

ethyl 4-(3-hydroxyphenyl)tetrahydro-2H-pyran-4-carboxylate

The product from Example 124A (0.74g, 2.17 mmol) in EtOH (2 mL) was treated with 10% Pd/C (0.34 g) under an atmosphere of hydrogen overnight. The mixture was filtered through celite and a 0.2 micron filter and evaporated in vacuo to provide 0.49 grams (90%) of the title compound as a white solid. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.2 (t, 3, J= 7.5), 1.9-2.04 (m, 2), 2.5 (dd, 2, J=12, 3), 3.58 (dt, 2, J=10.5, 3), 3.98 (dt, 2, J=10.5, 3), 4.06 (q, 2, J= 7.5), 5.08 (s,1), 6.75 (d, 1, J=9), 6.88 (m,1), 6.95 (d, 1, J=9), 7.25 (t, 1, J=9); MS (APCI+) m/z 341 $(M+H)^+$.

Example 124C

ethyl 4-[3-({4-[[(diethylamino)carbonyl](methyl)amino]benzyl}oxy)phenyl]tetrahydro-2H-pyran-4-carboxylate

The product from Example 124B (0.078 g, 0.26 mmol) in 1mL of DMF was treated with solid sodium hydride (0.007g, 0.28 mmol) at ambient temperature. After stirring for 30 minutes, the reaction mixture was treated with the product from Example 123D (0.06 g, 0.24 mmol) in 0.5 mL. The mixture was stirred overnight. The mixture was quenched with water and saturated aqueous $NH_4Cl$ (3 mL) and extracted with diethyl ether and ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and

concentrated to provide an oily residue (0.109 g), which was chromatographed on silica gel (80:20 hexanes: acetone) to provide 0.027 grams (24%) of the title compound as a glassy solid. $^1$H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 6, J=7.5), 1.2 (t, 3, J=7.5), 1.9-2.04 (m, 2), 2.48-2.55 (m, 2), 3.09-3.16 (m, 7), 3.5-3.62 (dt, 2, J=10.5, 3), 3.88-3.97 (dt, 2, J=10.5, 3), 4.05 (q, 2, J=7.5), 5.0 (s, 2), 6.9 (dt, 1, J=12, 2), 6.98-7.05 (m, 2), 7.1 (d, 2, J=9), 7.25 (m,1), 7.1 (d, 2, J=9); MS (APCI+) m/z 469 $(M+H)^+$.

Example 125

N,N-diethyl-N'-(4-{[3-fluoro-5-(1-hydroxycyclohexyl)phenoxy]methyl}phenyl)-N'-methylurea

Example 125A

1-[3-(benzyloxy)-5-fluorophenyl]cyclohexanol

The product from Example 128A and cyclohexanone were processed as described in Example 128B to provide the title compound.

Example 125B

3-fluoro-5-(1-hydroxycyclohexyl)phenol

The product from Example 125A was processed as described in Example 126C to provide the title compound.

Example 125C

N,N-diethyl-N'-(4-{[3-fluoro-5-(1-hydroxycyclohexyl)phenoxy]methyl}phenyl)-N'-methylurea

The product from Example 125B (0.17 g, 0.81 mmol) in 3 mL of DMF was treated with solid sodium hydride (0.048 g, 2.0 mmol) at ambient temperature. After stirring for 20 minutes, the reaction mixture was treated with the product from Example 123D (0.22 g, 1.05 mmol) in 2 mL of DMF and allowed to stir overnight. The mixture was quenched with water and saturated aqueous ammonium hydroxide (5 mL) and extracted with diethyl ether and

ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated to provide an oily residue (0.2 g), which was chromatographed on silica gel (80:20 hexanes:acetone) to provide 0.065 grams (19%) of the title compound as a white solid. $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.98 (m, 6), 1.64-1.81 (m, 10), 3.08-3.18 (m, 4), 3.21 (s, 3), 5.0 (s, 2), 6.55 (dt, 1, J=10.5, 3), 6.8 (dt, 1, J=10.5, 3), 6.92 (m,1), 7.1 (d, 2, J=7.5), 7.38 (d, 2, J=7.5); MS (APCI+) m/z 463 ( $M+Cl)^+$.

Example 126

N-{4-[(3-fluoro-5-tetrahydro-2H-pyran-4-ylphenoxy)methyl]phenyl}-N,2-dimethyl-1-pyrrolidinecarboxamide

Example 126A

4-[3-(benzyloxy)-5-fluorophenyl]tetrahydro-2H-pyran-4-ol

The product from Example 128A and tetrahydro-4H-pyran-4-one were processed as described in Example 128B to provide the title compound.

Example 126B

4-[3-(benzyloxy)-5-fluorophenyl]tetrahydro-2H-pyran

The product from Example 126A (250 mg, 0.83 mmol) in 5 mL of trifluoroacetic acid and 1 mL of $CH_2Cl_2$ was treated with triethylsilane (5 mL). After 10 hours, the mixture was concentrated in vacuo and the crude material was purified by column chromatography ($CHCl_3$) to provide 102 mg (43%) of a colorless oil. $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.60-1.70 (m, 4), 2.62 (m, 1), 3.40 (m, 2), 3.97 (m, 2), 4.93 (s, 2), 6.46 (m, 2), 6.56 (t, 1, J=2.1), 7.20-7.35 (m, 5); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 34.5, 42.3, 69.0, 71.1, 100.9 (d), 107.0 (d), 110.3 (d), 128.3, 128.9, 129.4, 137.3, 149.8 (d), 160.9 (d), 165.7; HRMS calcd for $C_{18}H_{19}FO_2$: 286.1369; found 286.1367.

Example 126C

3-fluoro-5-tetrahydro-2H-pyran-4-ylphenol

The product from Example 126B (100 mg) in 10 mL of ethanol was treated with 10% Pd/C under an atmosphere of hydrogen for 5 hours. The mixture was filtered through a plug of celite and concentrated in vacuo to provide the title compound. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.70 (m, 4), 2.70 (m, 1), 3.55 (m, 2), 4.00 (dt, 2, J=11.2, 3.0), 6.32 (dt, 1, J=10.5, 2.2), 6.44 (dt, 1, J=10.2, 1.7), 6.48 (t, 1, J=1.7).

Example 126D

N-{4-[(3-fluoro-5-tetrahydro-2H-pyran-4-ylphenoxy)methyl]phenyl}-N,2-dimethyl-1-pyrrolidinecarboxamide

The product from Example 126C (34 mg, 0.17 mmol) and the product from Example 47A (80 mg, 0.26 mmol) in 1 mL of DMF were treated with sodium hydride (16 mg, 0.67 mmol). After 2 hours, the mixture was partitioned between diethyl ether and water. The phases were separated and the organic phase was washed with water and concentrated in vacuo. The crude material was purified by column chromatography (200:1 $CHCl_3$:MeOH) to provide 45 mg (62%) of the title compound. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.16 (d, 2, J=6.0), 1.26 (m, 1), 1.55 (m, 2), 1.68 (m, 4), 1.92 (m, 1), 2.56 (m, 1), 2.64 (m, 1), 3.00 (dq, 1, J=10.6, 3.0), 3.16 (s, 3), 3.43 (m, 2), 3.90 (sext, 1, J=6.8), 4.00 (dt, 2, J=11.4, 3.0), 4.91 (s, 2), 6.48 (m, 2), 6.57 (t, 1, J=1.7), 7.06 (d, 2, J=8.7), 7.30 (d, 2, J=8.7); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 20.0, 24.8, 29.6, 33.6, 39.0, 41.5, 49.1, 54.0, 100.0 (d), 106.2 (d), 109.4 (d), 124.5, 128.6, 132.2, 149.0 (d), 159.9 (d), 161.0 (d), 164.8; IR 2924, 2852, 1644, 1612, 1381 $cm^{-1}$; HRMS calcd for 427.2397, found 427.2392.

Example 127

N,N-diethyl-N'-{4-[(3-fluoro-5-tetrahydro-2H-pyran-4-ylphenoxy)methyl]phenyl}-N'-methylurea

The product from Example 123D (78 mg, 0.26 mmol) and the product from Example 126C (38 mg, 0.19 mmol) were processed as described in Example 126D. The resultant crude material was purified by column chromatography (200:1 $CHCl_3$:MeOH) to afford 38 mg (48%) of the title compound. $^1$H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 6, J=7.2), 1.68 (m,

4), 2.63 (m, 1), 3.06 (q, 4, J=7.2), 3.10 (s, 3), 3.43 (m, 2), 4.00 (m, 2), 4.92 (s, 2), 6.46 (m, 2), 6.56 (m, 1), 7.02 (d, 2, J=8.6), 7.30 (d, 2, J=8.6); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 12.9, 29.7, 33.6, 41.5, 42.1, 68.1, 69.8, 100.1 (d), 106.2 (d), 109.5 (d), 123.7, 128.7, 132.4, 149.0 (d), 159.9 (d), 162.0 (d), 164.8; IR 1649, 1614, 1458 $cm^{-1}$; HRMS calcd for 415.2397, found 415.2377.

Example 128

tert-butyl 4-[3-({4-[[(diethylamino)carbonyl](methyl)amino]benzyl}oxy)-5-fluorophenyl]-4-hydroxy-1-piperidinecarboxylate

Example 128A

1-(benzyloxy)-3-bromo-5-fluorobenzene

Benzyl alcohol and 1-bromo-3,5-difluorobenzene were processed as described in Example 15D to provide the title compound.

Example 128B

tert-butyl 4-[3-(benzyloxy)-5-fluorophenyl]-4-hydroxy-1-piperidinecarboxylate

The Grignard reagent prepared from magnesium turnings (0.75 g, 28.5 mmol), a few drops of 1,2-dibromoethane, a crystal of iodine, and the product from Example 128A (8 g, 28.5 mmol) in dry diethyl ether (50 mL) was treated with tert-butyl 4-oxo-1-piperidinecarboxylate (6.25 g, 31.4 mmol) in diethyl ether (100 mL) dropwise. The mixture was stirred overnight and then partitioned between diethyl ether and saturated aqueous $NH_4Cl$. The combined organic phases were washed with brine, water, dried over $MgSO_4$, and evaporated in vacuo to provide 7.2 grams (65%) of the title compound as a white crystalline solid. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.5 (s, 9), 1.58-1.62 (m, 2), 1.88-2.0 (m, 2), 3.1-3.29 (m, 2), 3.98-4.12 (br m, 2), 5.05 (s, 2), 6.6 (dt, 1, J=10.5, 2), 6.78 (dt, 1, J=10.5, 2), 6.9 (m, 1), 7.34-7.45 (m, 5); MS (APCI+) m/z 302 ( M+H-Boc)$^+$.

Example 128C

tert-butyl 4-(3-fluoro-5-hydroxyphenyl)-4-hydroxy-1-piperidinecarboxylate

The product from Example 128B was processed as described in Example 126C to provide the title compound.

Example 128D

tert-butyl 4-[3-({4-[[(diethylamino)carbonyl](methyl)amino]benzyl}oxy)-5-fluorophenyl]-4-hydroxy-1-piperidinecarboxylate

The product from Example 128C (0.9 g, 3.81 mmol) in 6 mL of DMF was treated with solid sodium hydride (0.2 g, 8.33 mmol) at ambient temperature. After 30 minutes of stirring, the reaction mixture was treated with the product from Example 123D (1.3 g, 4.15 mmol) in 2 mL of DMF. The mixture was heated at 75 °C overnight. After cooling to ambient temperature, the mixture was quenched with water and saturated aqueous $NH_4Cl$ (3 ml), and extracted with diethyl ether and ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated to provide an oily residue (0.9 g), which was chromatographed on silica gel (70 :30 hexanes:acetone) to provide 0.26 grams (13%) of the title compound as a white solid. $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 6, J=7), 1.5 (s, 9), 1.62-1.74 (m, 2), 1.88-2.2 (m, 2), 3.06-3.3 (m, 9), 3.98-4.11 (br m, 2), 5.0 (s, 2), 6.58 (dt, 1, J=10.5, 3), 6.8 (dt, 1, J=10.5, 2), 6.9 (bs,1), 7.1 (d, 2, J=7.5), 7.38 (d, 2, J=7.5); MS (APCI+) m/z 530 $(M+H)^+$.

Example 129

5-{[3-(1-benzyl-4-hydroxy-4-piperidinyl)-5-fluorophenoxy]methyl}-1,3-dimethyl-1,3-dihydro-2H-benzimidazol-2-one

Example 129A

methyl 2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylate

Methyl 3,4-diaminobenzoate (1.8 g, 10.85 mmol) in 20 mL of THF:DMF (1:1) was treated with 1,1'-carbonyldiimidazole (1.95 g, 11.95 mmol). A pale white solid slowly

precipitated during overnight stirring. The solid was filtered, washed with a small amount of THF, and dried in vacuo to provide 1.75 g (84%) of the title compound. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 3.83 (s, 3), 7.02 (d, 1, J=7.5), 7.48 (dd, 1, J=7.5, 2.0), 7.64 (dd, 1, J=7.5, 2.0), 10.92 (br s,1), 11.05 (br s,1); MS (DCI/$NH_3$) 193 $(M+H)^+$; 210 $(M+NH_4)^+$.

Example 129B

methyl 1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylate

The product from Example 129A (10.2 g, 53.13 mmol) in 300 mL of THF:DMF (1:3) was treated with sodium hydride (2.8 g, 117 mmol). After 20 minutes, the suspension was treated with methyl iodide (8 mL) via syringe and the reaction monitored by TLC (hexane:acetone 3:2). The reaction mixture was diluted with water and extracted with an excess of diethyl ether. The combined organic phases were washed with 100 mL of brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to provide 9.8 g (84%) of the title compound. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 3.34 (s, 3), 3.38 (s, 3), 3.85 (s, 3), 7.25 (d, 1, J=7.5), 7.69 (d, 1, J=2.0), 7.77 (dd, 1, J=7.5, 2.0); MS (APCI+) m/z 221 $(M+H)^+$.

Example 129C

5-(hydroxymethyl)-1,3-dimethyl-1,3-dihydro-2H-benzimidazol-2-one

The product from Example 129B (10 g, 45.5 mmol) in 350 mL of THF and 2 mL of MeOH was treated with lithium borohydride (5 g, 229 mmol) and then refluxed for 3 hours. After cooling on ice, the mixture was slowly quenched by the addition of saturated aqueous $NH_4Cl$ followed by addition of water. The mixture was extracted with ethyl acetate (1.5 L) and the combined organic layers were washed with 1N HCl, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to provide 6.9 g (79%) of the title compound as a solid. $^1$H NMR (300 MHz, $CDCl_3$) δ 3.42 (s, 6), 4.74 (s, 2), 6.92 (d, 1, J=7.5), 7.05 (s, 1), 7.08 (d, 1, J=7.5); $^1$H NMR (300 MHz, DMSO-$d_6$) δ 3.34 (s, 6), 4.52 (d, 2, J=6.0), 5.15 (t, 1, J=6.0), 7.02 (d, 1, J=7.5), 7.08 (d, 1, J=2.0), 7.11(s, 1); MS (DCI/$NH_3$) m/z 193 ( $M+H)^+$; 210 $(M+NH_4)^+$.

Example 129D

1-benzyl-4-(3,5-difluorophenyl)-4-piperidinol

A solution of the Grignard reagent, prepared from 1-bromo-3,5-difluorobenzene (10 g, 51.8 mmol), three drops of 1,2-dibromoethane, one crystal of iodine, and magnesium turnings (1.35 g, 56.25 mmol) in dry diethyl ether (60 mL), was treated with a solution of 1-benzyl-4-piperidinone (10.1 g, 53.5 mmol) in diethyl ether (60 mL) dropwise at ambient temperature. The mixture was stirred overnight and then partitioned between diethyl ether and saturated aqueous $NH_4Cl$. The organic phase was washed with brine, water, dried over $MgSO_4$, and concentrated in vacuo to provide the title compound (6.1 g, 38%) as a solid. $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.72 (m, 2), 2.05-2.2 (dt, 2, J=12, 3), 2.4-2.5 (dt, 2, J=10.5, 3), 2.75-2.95 (br d, 2, J=10.5), 3.6 (s, 2), 6.69 (tt, 1, J=10.5, 3), 7.04 (m, 2 ), 7.28-7.4 (m, 5); MS (APCI+) m/z 303 ( $M+H)^+$.

Example 129E

5-{[3-(1-benzyl-4-hydroxy-4-piperidinyl)-5-fluorophenoxy]methyl}-1,3-dimethyl-1,3-dihydro-2H-benzimidazol-2-one

The product from Example 129C (0.5 g, 2.6 mmol) in 5 mL of DMF was treated with sodium hydride (0.190 g, 7.9 mmol) at ambient temperature. The resulting mixture was stirred for 30 minutes and then treated with a solution of the product from Example 129D (0.91 g, 3 mmol) in 3 mL of DMF. The mixture was heated at 60 °C overnight. After cooling to ambient temperature, the mixture was quenched with water and saturated aqueous $NH_4Cl$ (3 mL), and extracted with diethyl ether and ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated to provide a solid, which was crystallized from MeOH and ethyl acetate to provide 0.72 g (58%) of the title compound as a solid. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 1.68-1.85 (m, 2), 2.26-2.48 (m, 2), 3.2-3.3 (m, 4), 3.31-3.42 (m, 6), 4.36 (m, 2), 5.1 (s, 2), 6.78-6.88 (m, 2), 6.92 (br s,1), 7.10-7.22 (m, 3), 7.42-7.54 (m, 5); MS (APCI+) m/z 476 $(M+H)^+$.

Example 130

5-{[3-(trans-1,4-dimethoxycyclohexyl)-5-fluorophenoxy]methyl}-1,3-dimethyl-1,3-dihydro-2H-benzimidazol-2-one

The title compound [Registry Number 155821-58-2] was prepared according to the procedure described in WO 94/05638.

Example 131

5-{[3-fluoro-5-(8-hydroxy-1,4-dioxaspiro[4.5]dec-8-yl)phenoxy]methyl}-1,3-dimethyl-1,3-dihydro-2H-benzimidazol-2-one

Example 131A

8-(3,5-difluorophenyl)-1,4-dioxaspiro[4.5]decan-8-ol

The Grignard reagent prepared from magnesium turnings (1.3 g, 53.5 mmol), 1-bromo-3,5-difluorobenzene (10 g, 51.8 mmol), and several drops of 1,2-dibromoethane in 100 mL of diethyl ether was treated with 1,4-dioxaspiro[4.5]decan-8-one (8.2 g, 52.6 mmol) in 100 mL of diethyl ether over 1 hour dropwise. After 16 hours, the mixture was quenched by the addition of 200 mL of saturated aqueous $NH_4Cl$. The phases were separated and the organic phase was concentrated in vacuo. The crude material was crystallized from 20 mL of hot ethyl acetate to provide 8.6 grams (61%) of the title compound as a white solid. $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.70 (m, 4), 2.05 (m, 4), 2.32 (br s, 1), 3.95 (s, 4), 6.66 (tt, 1, J=8.7, 2.3), 7.04 (m, 2); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 30.5, 36.3, 64.1, 64.2, 72.2, 102.0, 108.1 (m), 153.2 (t), 161.7 (d), 164.1 (d); IR 3513, 1625, 1595, 1439 $cm^{-1}$; Anal calcd for $C_{14}H_{16}F_2O_3$: C, 62.22; H, 5.97; found: C, 62.38; H, 5.93.

Example 131B

5-{[3-fluoro-5-(8-hydroxy-1,4-dioxaspiro[4.5]dec-8-yl)phenoxy]methyl}-1,3-dimethyl-1,3-dihydro-2H-benzimidazol-2-one

The product from Example 129C (0.2 g, 1.05 mmol) in 5 mL of DMF was treated with sodium hydride (0.075 g, 3.1 mmol) at ambient temperature. After stirring for 30

minutes, the mixture was treated with the product from Example 131A (0.3 g, 1.1 mmol) in 1.5 mL of DMF. The mixture was heated at 60 °C overnight. After cooling to ambient temperature, the mixture was quenched with water and saturated aqueous $NH_4Cl$ (3 mL), and extracted with diethyl ether and ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to provide an oily residue which was chromatographed on silica gel (60:40 hexane:acetone) to provide 0.16g (32%) of the title compound as a white solid. $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.71(d, 2, J=10.5), 1.78 (d, 2, J=10.5), 2.0-2.2 (m, 4), 3.45 (2s, 6), 3.98-4.05 (m, 4), 5.08 (m, 2), 6.6 (dt, 1, J=10.5, 3), 6.85 (dt, 1, J=10.5, 3), 6.98 (m, 2), 7.08 (s,1), 7.15 (d, 1, J=9); MS: APCI ( M+Cl-neg.ion) 477; FAB (HRMS) calculated for $C_{24}H_{28}O_5N_2F$: 443.1982. Found: 443.1966.

Example 132

5-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}-1,3-dimethyl-1,3-dihydro-2H-benzimidazol-2-one

The product from Example 129C (0.2 g, 1.05 mmol) in 5 mL of DMF was treated with solid sodium hydride (0.075 g, 3.1 mmol) at ambient temperature. After stirring for 30 minutes, the reaction mixture was treated with the product from Example 131A (0.3 g, 1.1 mmol) in 1.5 mL of DMF and then heated at 60 °C overnight. After cooling to ambient temperature, the mixture was quenched with water and saturated aqueous $NH_4Cl$ (3 mL), and extracted with diethyl ether and ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to provide an oily residue (0.2 g), which was chromatographed on silica gel (60:40 hexanes:acetone) to provide 0.16 g (32%) of the title compound as a white solid. $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.71(d, 2, J=10.5), 1.78 (d, 2, J=10.5), 2.0-2.2 (m, 4), 3.45 (2s, 6), 3.98-4.05 (m, 4), 5.08 (m, 2), 6.6 (dt, 1, J=10.5, 3), 6.85 (dt, 1, J=10.5, 3), 6.98 (m, 2), 7.08 (s,1), 7.15 (d, 1, J=9); MS (APCI-) m/z ( M-H+Cl)$^-$ 477; FAB HRMS: calculated for: $C_{24}H_{28}O_5N_2F$: 443.1982. Found: 443.1966.

Example 133

N-allyl-N'-(4-{[3-(trans-1,4-dimethoxycyclohexyl)-5-fluorophenoxy]methyl}phenyl)-N,N'-dimethylurea

Example 133A

methyl 4-{[(allylamino)carbonyl]amino}benzoate

Methyl 4-aminobenzoate (19.7 g, 130 mmol) in 100 mL of THF was treated with allylisocyanate (18 mL, 204 mmol), refluxed for 16 hours, and then concentrated in vacuo. The crude material was crystallized from 500 mL of hot ethyl acetate to afford 23.9 g (79%) of the title compound as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 3.68 (br s, 1), 3.83 (m, 2), 3.87 (s, 3), 5.10 (br d, 1, J=8.9), 5.20 (br d, 1, J=17.3), 5.85 (m, 1), 7.43 (m, 2), 7.90 (m, 2); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 41.9, 51.6, 115.3, 117.3, 122.9, 130.6, 134.6, 144.1, 155.6, 167.2; IR 3372, 1678, 1590, 1531 cm$^{-1}$; Anal calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96; found: C, 61.74; H, 6.11: N, 12.04.

Example 133B

methyl 4-[{[allyl(methyl)amino]carbonyl}(methyl)amino]benzoate

The product from Example 133A (1.08 g, 4.62 mmol) in 15 mL of DMF was treated with $CsCO_3$ (4.4 g, 13.5 mmol) and methyl iodide (1 mL, 16.1 mmol). After 3 days at ambient temperature, the mixture was partitioned between 50 mL of diethyl ether and 50 mL of water and the phases were separated. The organic phase was washed with water, dried over $Na_2SO_4$, and concentrated in vacuo. The crude material was purified by column chromatography (80:20 hexanes:ethyl acetate) to provide 436 mg (36%) of the title compound. $^1$H NMR (400 MHz, $CDCl_3$) δ 2.62 (s, 3), 3.26 (s, 3), 3.80 (br d, 2, J=6.3), 3.90 (s, 3), 5.14 (m, 2), 5.72 (ddt, 1, J=16.5, 10.6, 6.3), 7.06 (d, 2, J=8.9), 7.98 (d, 2, J=8.9); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 35.3, 38.3, 51.9, 52.5, 117.8, 120.9, 124.6, 130.9, 132.9, 150.4, 160.8, 166.4; IR 1719, 1655, 1606 cm$^{-1}$; Anal calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.37; H, 6.81; N, 10.39.

Example 133C

N-allyl-N'-[4-(hydroxymethyl)phenyl]-N,N'-dimethylurea

The product from Example 133B (3.75 g, 14.3 mmol) in 50 mL of diethyl ether was cooled to 0 °C and treated with lithium aluminum hydride (595 mg, 15.7 mmol). After 3 hours at 0 °C, the cooling bath was removed and stirring continued for an additional 2 hours. The reaction mixture was quenched by the successive addition of 0.6 mL of water, 0.6 mL of 2N NaOH, and 1.8 mL of water The mixture was partitioned between 1N HCl and diethyl ether and the phases were separated. The organic phase was washed with water and concentrated in vacuo to give 1.6 g (48%) of the title compound, which was used without further purification. $^1$H NMR (400 MHz, $CDCl_3$) δ 2.55 (s, 3), 3.20 (s, 3), 3.75 (d, 2, J=6.3), 4.68 (s, 3), 5.10 (m, 2), 5.64 (ddt, 1, J=16.5, 10.6, 6.3), 7.08 (d, 2, J=8.5), 7.34 (d, 2, J=8.5).

Example 133D

N-allyl-N'-[4-(bromomethyl)phenyl]-N,N'-dimethylurea

The product from Example 133C (647 mg, 2.76 mmol) in 30 mL of $CCl_4$ was cooled to 0 °C and treated with pyridine (110 μL, 1.36 mmol) and then $PBr_3$ (520 μL, 5.53 mmol). After 20 minutes, the cooling bath was removed and the reaction mixture was allowed to stir for 10 minutes at ambient temperature. The white mixture was partitioned between methylene chloride and water and the phases were separated. The organic phase was washed with water and concentrated in vacuo to provide 800 mg of the title compound as a colorless oil, which was used without further purification. $^1$H NMR (400 MHz, $CDCl_3$) δ 2.55 (s, 3), 3.18 (s, 3), 3.75 (d, 2, J=5.9), 4.40 (s, 2), 5.10 (m, 2), 5.64 (m, 1), 7.11 (d, 2, J=8.5), 7.35 (d, 2, J=8.1).

Example 133E

3-(trans-1,4-dimethoxycyclohexyl)-5-fluorophenol

The title compound was prepared using the procedure described in US 5,407,959.

Example 133F

N-allyl-N'-(4-{[3-(trans-1,4-dimethoxycyclohexyl)-5-fluorophenoxy]methyl}phenyl)-N,N'-dimethylurea

Sodium hydride (18 mg, 0.45 mmol) in 0.5 mL of DMF was treated with the product from Example 133E (50 mg, 0.20 mmol) in 0.5 mL of DMF. After stirring for 2 hours at ambient temperature, the product from Example 133D (57 mg, 0.19 mmol) in 1 mL of DMF was added to the reaction mixture. After 2 hours at ambient temperature, the mixture was partitioned between ethyl acetate and water and the phases separated. The organic phase was washed with water and concentrated in vacuo. The crude material was purified by column chromatography (99:1 $CHCl_3$:MeOH) to provide 61 mg (68%) of the title compound as a clear oil. $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.81 (m, 6), 1.95 (m, 2), 2.56 (s, 3), 2.98 (s, 3), 3.21 (s, 3), 3.32 (s, 3), 3.50 (m, 1), 3.75 (m, 2), 5.0 (m, 2), 5.10 (m, 2), 5.64 (m, 1), 6.57 (dt, 1, J=10.4, 2.2), 6.75 (ddd, 1, J=10.0, 2.4, 1.2), 6.84 (m, 1), 7.06 (d, 1, J=8.4), 7.10 (d, 2, J=8.4), 7.30 (d, 1, J=8.4), 7.38 (d, 2, J=8.4); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 25.1, 29.4, 35.5, 39.6, 52.7, 55.6, 69.8, 74.2, 100.8 (d), 105.9 (d), 108.7 (d), 117.4, 123.8, 128.7, 132.4, 133.4, 146.7, 149.3, 159.8 (d), 162.0 (d), 164.8.

Example 134

N-(4-{[3-(trans-1,4-dimethoxycyclohexyl)-5-fluorophenoxy]methyl}phenyl)-N',N'-diethyl-N-methylurea

The product from Example 133E (90 mg, 0.35 mmol) in 1 mL of DMF was treated with sodium hydride (22 mg, 0.92 mmol) and then the product from Example 123D (120 mg, 0.40 mmol) in 1 mL of DMF via cannula. The resultant brown slurry was stirred at ambient temperature for 2 hours and then partitioned between diethyl ether and water. The phases were separated and the organic phase was washed with water and concentrated in vacuo. The crude material was purified by column chromatography (98:2 $CHCl_3$:MeOH) to provide 87 mg (84%) of the title compound. $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.95 (t, 6, J=7.1), 1.8 (m, 6), 1.95 (m, 2), 3.12 (q, 4, J=7.1), 3.16 (s, 3), 3.32 (s, 3), 3.50 (m, 1), 5.00 (s, 2), 6.57 (dt, 1, J=10.2, 2.2), 6.75 (dt, 1, J=10.2, 1.7), 6.84 (br s, 1), 7.10 (d, 2, J=8.5), 7.38 (d, 2, J=8.5); $^{13}C$

NMR (100 MHz, $CDCl_3$) δ 12.9, 25.1, 29.4, 39.7, 42.0, 50.1, 55.7, 65.8, 69.8, 74.2, 101.0 (d), 105.9 (d), 108.8 (d), 123.7, 128.7, 132.3, 147.2, 149.3 (d), 159.8 (d), 161.8 (d), 165.3; IR 2933, 1651, 1613, 1587, 1432 $cm^{-1}$; Anal calcd for $C_{27}H_{37}FN_2O_4F$: C, 68.62; H, 7.89; N, 5.93. Found: C, 68.38; H, 7.90; N, 5.88.

Example 135

N-(4-{[3-fluoro-5-(4-morpholinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide

The product from Example 15D (125 mg, 0.30 mmol) in 1.5 mL of degassed toluene was treated with $Pd(dba)_2$ (19 mg, 0.033 mmol), BINAP (59 mg, 0.095 mmol), morpholine (50 μL, 0.46 mmol) and sodium tert-butoxide (72 mg, 0.75 mmol). The mixture was heated to 60 °C for 18 hours and then cooled and partitioned between ethyl acetate and water. The phases were separated and the organic phase was washed with water and concentrated in vacuo. The crude material was purified by column chromatography (99:1 $CHCl_3$:MeOH) to provide 86 mg (67%) of the title compound. $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.23 (d, 3, J=6.4), 1.34 (m, 1), 1.55-1.65 (m, 2), 2.0 (m, 1), 2.62 (m, 1), 3.07 (m, 1), 3.13 (m, 4), 3.22 (s, 3), 3.82 (m, 4), 3.97 (m, 1), 4.97 (s, 2), 6.20 (m, 2), 6.30 (m, 1), 7.12 (d, 2, J=8.0), 7.35 (d, 2, J=8.0); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 20.0, 24.8, 33.3, 39.0, 48.7, 49.1, 54.0, 66.6, 69.8, 93.3 (d), 95.5 (d), 98.2 (d), 124.5, 128.6, 132.3, 146.4, 153.1 (d), 159.5, 161.4 (d), 165.6; IR 2964, 1627, 1585 $cm^{-1}$; Anal calcd for $C_{24}H_{30}FN_3O_3$: C, 67.43; H, 7.07; N, 9.83. Found: C, 67.81; H, 7.33; N, 9.47.

Example 136

(-) N-(4-{[3-fluoro-5-(4-morpholinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide

The enantiomers from Example 135 were separated by chiral HPLC (Daicel OJ column, 90:10 hexanes:EtOH). $[\alpha]^{23}_D$ -177° (c 0.09, $CH_2Cl_2$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.23 (d, 3, J=6.4), 1.34 (m, 1), 1.55-1.65 (m, 2), 2.0 (m, 1), 2.62 (m, 1), 3.07 (m, 1), 3.13 (m, 4), 3.22 (s, 3), 3.82 (m, 4), 3.97 (m, 1), 4.97 (s, 2), 6.20 (m, 2), 6.30 (m, 1), 7.12 (d, 2, J=8.0),

7.35 (d, 2, J=8.0); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 20.0, 24.8, 33.3, 39.0, 48.7, 49.1, 54.0, 66.6, 69.8, 93.3 (d), 95.5 (d), 98.2 (d), 124.5, 128.6, 132.3, 146.4, 153.1 (d), 159.5, 161.4 (d), 165.6; IR 2964, 1627, 1585 cm$^{-1}$.

Example 137

(2R)-N-(4-{[3-fluoro-5-(4-morpholinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide

The enantiomers from Example 135 were separated by chiral HPLC (Daicel OJ column, 90:10 hexanes:EtOH). $[\alpha]^{23}_D$ +199° (c 0.13, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.23 (d, 3, J=6.4), 1.34 (m, 1), 1.55-1.65 (m, 2), 2.0 (m, 1), 2.62 (m, 1), 3.07 (m, 1), 3.13 (m, 4), 3.22 (s, 3), 3.82 (m, 4), 3.97 (m, 1), 4.97 (s, 2), 6.20 (m, 2), 6.30 (m, 1), 7.12 (d, 2, J=8.0), 7.35 (d, 2, J=8.0); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 20.0, 24.8, 33.3, 39.0, 48.7, 49.1, 54.0, 66.6, 69.8, 93.3 (d), 95.5 (d), 98.2 (d), 124.5, 128.6, 132.3, 146.4, 153.1 (d), 159.5, 161.4 (d), 165.6; IR 2964, 1627, 1585 cm$^{-1}$.

Example 138

N,N-diethyl-N'-(4-{[3-fluoro-5-(4-morpholinyl)phenoxy]methyl}phenyl)-N'-methylurea

The product from Example 1E (101 mg, 0.25 mmol), $Pd(dba)_2$ (14 mg, 0.024 mmol), BINAP (47 mg, 0.076 mmol), morpholine (40 μL, 0.36 mmol), and sodium tert-butoxide (60 mg, 0.63 mmol) were processed as described in Example 1F. The crude material was purified by column chromatography (99:1 $CHCl_3$:MeOH) to provide 103 mg (100%) of the title compound. $^1$H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, 6, J= 7.0), 3.10 (m, 8), 3.16 (s, 3), 3.80 (m, 4), 4.97 (s, 2), 6.22 (tt, 2, J=10.2, 2.1), 6.28 (m, 1), 7.08 (m, 2, J=8.4), 7.36 (d, 2, J=8.4); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 12.9, 39.6, 42.0, 48.7, 66.6, 69.7, 93.3 (d), 95.5 (d), 98.2 (d), 123.6, 128.6, 132.4, 147.2, 153.1 (d), 160.5 (d), 162.4 (d), 165.6; IR 2967, 1646, 1585 cm$^{-1}$.

Example 139

N-(4-{[3-fluoro-5-(2-methyl-3-oxo-1-piperazinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide

The product from Example 15D and 3-methyl-2-piperazinone were processed as described in Example 15E to provide the title compound as a yellow oil. MS (APCI+) m/z 455 $(M+H)^+$.

## Example 140

## (+) N-[4-({[6-(4-hydroxytetrahydro-2H-pyran-4-yl)-2-pyridinyl]oxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide

### Example 140A

### 4-(6-bromo-2-pyridinyl)tetrahydro-2H-pyran-4-ol

n-Butyllithium (3.55 mL, 8.9 mmol) in 15 mL of THF was cooled to -78 °C and treated dropwise with 2,6-dibromopyridine (2.0 g, 8.4 mmol) in 10 mL of THF. After 10 minutes, the reaction mixture was treated with tetrahydro-4H-pyran-4-one (1 mL, 10.8 mmol) dropwise. After 2 hours at -78 °C, the mixture was warmed to 0 °C for 2 hours and then partitioned between ethyl acetate and water. The phases were separated and the organic phase was concentrated in vacuo. The crude material was crystallized from 10 mL of ethyl acetate to provide 1.3 grams (60%) of the title compound as white crystals. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.60 (br d, 2, J=13.5), 2.12 (m, 2), 3.96 (m, 4), 4.22 (s, 1), 7.35 (dd, 1, J=7.8, 0.7), 7.42 (dd, 1, J=7.8, 0.7), 7.60 (t, 1, J=7.8); $^{13}$C NMR (75 Hz, $CDCl_3$) δ 38.2, 63.9, 70.5, 117.7, 126.6, 139.5, 140.7, 166.4; IR 3371, 1580, 1548 $cm^{-1}$; Anal calcd for $C_{10}H_{12}BrNO_2$: C, 46.53; H, 4.69; N, 5.43; found: C, 46.89; H, 4.63; N, 4.20.

### Example 140B

### (+) N-[4-({[6-(4-hydroxytetrahydro-2H-pyran-4-yl)-2-pyridinyl]oxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide

The product from Example 140A (98 mg, 0.38 mmol) in 1 mL of DMF at 0 °C was treated in succession with sodium hydride (34 mg, 1.4 mmol) and the product from Example 15C (103 mg, 0.42 mmol) in 1 mL of DMF via cannula. The cooling bath was removed and the mixture was warmed to 65 °C for 16 hours. The mixture was allowed to cool to ambient

temperature and then partitioned between ethyl acetate and water. The phases were separated and the organic phase was washed with water and concentrated in vacuo. The crude material was purified by column chromatography (200:1 $CHCl_3$:MeOH) to provide 98 mg (60%) of the racemate. The enantiomers were separated by chiral HPLC (Daicel OJ column, 90:10 hexanes:EtOH). $[\alpha]^{23}_D$ +131° (c 0.4, $CH_2Cl_2$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.24 (d, 3, J=6.4), 1.32 (m, 1), 1.56 (m, 2), 1.6-1.7 (m, 2), 2.00 (m, 2), 2.14 (dt, 2, J=12.2, 5.5), 2.62 (m, 1), 3.06 (m, 1), 3.22 (s, 3), 3.90 (m, 4), 4.44 (s, 1), 5.36 (s, 2), 6.74 (d, 1, J=8.1), 6.98 (d, 1, J=7.6), 7.12 (d, 2, J=8.4), 7.39 (d, 2, J=8.4), 7.65 (dd, 1, J= 7.6, 8.1); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 20.0, 24.8, 29.6, 33.3, 38.4, 49.1, 54.0, 64.1, 67.3, 70.4, 109.5, 111.4, 124.5, 128.7, 133.0, 140.0, 146.2, 159.6, 162.3, 162.5; IR 3403, 2960, 1623, 1609, 1578 $cm^{-1}$; HRMS calcd for $C_{24}H_{31}N_3O_4$ 425.2315; found 425.2308.

## Example 141

## (-) N-[4-({[6-(4-hydroxytetrahydro-2H-pyran-4-yl)-2-pyridinyl]oxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide

The title compound was isolated from the chiral chromatography described in Example 140B. $[\alpha]^{23}_D$ -121° (c 0.35, $CH_2Cl_2$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.24 (d, 3, J=6.4), 1.32 (m, 1), 1.56 (m, 2), 1.6-1.7 (m, 2), 2.00 (m, 2), 2.14 (dt, 2, J=12.2, 5.5), 2.62 (m, 1), 3.06 (m, 1), 3.22 (s, 3), 3.90 (m, 4), 4.44 (s, 1), 5.36 (s, 2), 6.74 (d, 1, J=8.1), 6.98 (d, 1, J=7.6), 7.12 (d, 2, J=8.4), 7.39 (d, 2, J=8.4), 7.65 (dd, 1, J=7.6, 8.1); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 20.0, 24.8, 29.6, 33.3, 38.4, 49.1, 54.0, 64.1, 67.3, 70.4, 109.5, 111.4, 124.5, 128.7, 133.0, 140.0, 146.2, 159.6, 162.3, 162.5; IR 3403, 2960, 1623, 1609, 1578 $cm^{-1}$.

## Example 143

## N,N-diethyl-N'-[4-({[6-(4-hydroxytetrahydro-2H-pyran-4-yl)-2-pyridinyl]oxy}methyl)phenyl]-N'-methylurea

The product from Example 140A (261 mg, 1.0 mmol), the product from Example 1D (227 mg, 0.95 mmol), and sodium hydride (80 mg, 3.33 mmol) were processed as described in Example 140B. The resultant crude material was purified by column chromatography

(99:1 $CHCl_3$:MeOH) to afford 220 mg (55%) of the title compound as a clear oil. $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.94 (t, 6, J=7.2), 1.58 (d, 2, J=12.3), 2.10 (dt, 2, J=12.7, 5.5), 3.11 (q, 4, J=7.2), 3.16 (s, 3), 3.90 (m, 4), 4.40 (s, 1), 5.35 (s, 3), 6.72 (d, 1, J=8.1), 6.97 (d, 1, J=7.2), 7.08 (d, 2, J=8.5), 7.40 (d, 2, J=8.5), 7.64 (t, 1, J=7.8); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 12.9, 38.5, 39.6, 42.0, 64.1, 67.3, 70.4, 109.6, 111.4, 123.6, 128.9, 133.0, 140.0, 147.0, 161.6, 162.3, 162.5; IR 3407, 2962, 1647, 1625 $cm^{-1}$; HRMS calcd for $C_{23}H_{31}N_3O_4$, 413.2315. Found 413.2314.

Examples 144-150

Examples 144 to 150 were prepared using the following procedure.

The product from Example 30F (659 mg, 1.48 mmol) in 5 mL of dry dioxane was treated with 4M HCl in dioxane (15 mL). After stirring for 1 hour at ambient temperature, the solvent was removed in vacuo and the resultant yellow oil residue was dried under vacuum at ambient temperature for 16 hours.

The crude hydrochloride salt was suspended in 10 mL of dry toluene, treated with triethylamine (4.04 mL, 29.0 mmol), stirred for 30 minutes at ambient temperature, and then filtered. The resulting clear yellow solution was transferred to eleven 20-mL screw-cap vials and cooled to 0 °C. The acid chlorides were added in excess (about 10 equivalents) and the resulting turbid yellow to dark yellow mixtures were stirred at 0 °C for 30 minutes and then allowed to warm up slowly to ambient temperature and stirred at ambient temperature for additional 5 hours. N,N-Diethylethylenediamine (0.387 mL, 2.69 mmol) was added to each vial and the mixtures were stirred at ambient temperature for 12 hours. The mixtures were each partitioned between 5% aqueous $NH_4Cl$ and ethyl acetate. Each organic layer was separated, washed with 5% aqueous $NH_4Cl$, saturated aqueous $NaHCO_3$, filtered through a silica gel sep-pak cartridge (Alltech 209150) and concentrated in vacuo to provide the crude product as yellow to dark yellow oils. The crude materials were purified by preparative HPLC (Waters Nova-Pak® HR C18 6 μm 60 □ 25x100 mm, 50-95% MeCN/10 mM $NH_4OAc$ over 10 min at 40 mL/min).

Example 144

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,3,3-trimethylbutanamide

The title compound was isolated as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.93 (s, 9), 1.90-2.01 (m, 4), 2.09 (br s, 2), 2.97 (s, 3), 3.24 (br s, 3), 3.74-3.87 (m, 4), 5.16 (s, 2), 6.72 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.87 (m, 1), 7.27 (d, 2, J=8.3), 7.55 (d, 2, J=8.3); MS (APCI+) m/z 444 $(M+H)^+$.

Example 145

2-ethyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylbutanamide

The title compound was isolated as a yellow solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.80 (t, 6, J=7.5), 1.37 (m, 2), 1.56 (m, 2), 1.89-2.01 (m, 4), 2.21 (m, 1), 2.97 (s, 3), 3.26 (s, 3), 3.73-3.87 (m, 4), 5.17 (s, 2), 6.74 (m, 2), 6.87 (m, 1), 7.28 (d, 2, J=8.3), 7.57 (d, 2, J=8.3); MS (APCI+) m/z 444 $(M+H)^+$.

Example 146

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2,2-trimethylpropanamide

The title compound was isolated as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.04 (s, 9), 1.89-2.00 (m, 4), 2.97 (s, 3), 3.20 (s, 3), 3.73-3.87 (m, 4), 5.17 (s, 2), 6.72 (dt, 1, J=10.4, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.32 (d, 2, J=8.3), 7.53 (d, 2, J=8.7); MS (APCI+) m/z 430 $(M+H)^+$.

Example 147

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylcyclopentanecarboxamide

The title compound was isolated as a yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.42 (m, 2), 1.63 (m, 2), 1.71 (m, 4), 1.88-2.01 (m, 4), 2.60 (m, 1), 2.97 (s, 3), 3.24 (br s, 3), 3.73-

3.87 (m, 4), 5.16 (s, 2), 6.74 (m, 2), 6.86 (m, 1), 7.30 (d, 2, J= 8.0), 7.56 (d, 2, J=8.0); MS (APCI+) m/z 442 $(M+H)^+$.

Example 148

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylcyclopropanecarboxamide

The title compound was isolated as a light yellow oil. $^1H$ NMR (500 MHz, $CD_3OD$) δ 0.67 (br d, 2, J= 4.1), 0.92 (m, 2), 1.42 (m, 1), 1.89-2.00 (m, 4), 2.96 (s, 3), 3.27 (br s, 3), 3.73-3.86 (m, 4), 5.16 (s, 2), 6.72 (dt, 1, J=10.5, 2.3), 6.75 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.38 (d, 2, J=8.3), 7.57 (d, 2, J=8.3); MS (APCI+) m/z 414 $(M+H)^+$.

Example 149

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2-dimethylpropanamide

The title compound was isolated as a yellow solid. $^1H$ NMR (500 MHz, $CD_3OD$) δ 1.00 (d, 6, J=7.0), 1.90-2.01 (m, 4), 2.53 (m, 1), 2.97 (s, 3), 3.23 (s, 3), 3.73-3.87 (m, 4), 5.17 (s, 2), 6.73 (dt, 1, J=10.5, 2.3), 6.76 (ddd, 1, J=10.1, 2.3, 1.5), 6.86 (m, 1), 7.31 (d, 2, J=8.1), 7.57 (d, 2, J=8.1); MS (APCI+) m/z 416 $(M+H)^+$.

Example 150

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-2-furamide

The title compound was isolated as a light yellow oil. $^1H$ NMR (500 MHz, $CD_3OD$) δ 1.91-2.02 (m, 4), 2.98 (s, 3), 3.42 (s, 3), 3.74-3.87 (m, 4), 5.17 (s, 2), 5.98 (br d, 1, J=3.6), 6.30 (dd, 1, J=3.6, 1.7), 6.71 (dt, 1, J=10.5, 2.3), 6.77 (ddd, 1, J=10.1, 2.3, 1.5), 6.88 (m, 1), 7.30 (d, 2, J=8.6), 7.44 (dd, 1, J=1.7, 0.7), 7.54 (d, 2, J=8.6); MS (APCI+) m/z 440 $(M+H)^+$.

Examples 151 and 152

Examples 151 and 152 were prepared using the following procedure.

The product from Example 30F (606 mg, 1.36 mmol) in 5 mL of dry dioxane was treated with 4M HCl in dioxane (15 mL). After stirring for 1 hour at ambient temperature, the solvent was removed in vacuo and the resultant yellow oil residue was dried under vacuum at ambient temperature for 16 hours.

The crude hydrochloride salt was suspended in 10 mL of dry toluene, treated with triethylamine (3.80 mL, 27.6 mmol), stirred for 30 minutes at ambient temperature, and then filtered. The resulting clear yellow solution was transferred to ten 20-mL screw-cap vials. Chloroformates were added in excess (about 10 equivalents) and the mixtures were stirred at ambient temperature for 24 hours. N,N-Diethylethylenediamine (0.387 mL, 2.69 mmol) was added to each vial and the mixtures were stirred at ambient temperature for 4 hours. The mixtures were each partitioned between 5% aqueous $NH_4Cl$ and EtOAc. Each organic layer was separated, washed with 5% aqueous $NH_4Cl$, saturated aqueous $NaHCO_3$, filtered through a silica gel sep-pak cartridge (Alltech 209150), and concentrated in vacuo to provide the crude materials as yellow to dark yellow oils. The crude materials were purified by preparative HPLC (Waters Nova-Pak® HR C18 6 μm 60 □ 25x100 mm, 50-95% MeCN/10 mM $NH_4OAc$ over 10 min at 40 mL/min).

Example 151

isopropyl 4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl(methyl)carbamate

The title compound was isolated as a light yellow oil. $^1H$ NMR (500 MHz, $CD_3OD$) δ 1.22 (d, 6, J=6.3), 1.90-2.01 (m, 4), 2.96 (s, 3), 3.27 (s, 3), 3.74-3.87 (m, 4), 4.91 (hept, 1, J=6.3), 5.11 (s, 2), 6.70 (dt, 1, J=10.5, 2.3), 6.74 (ddd, 1, J=10.1, 2.3, 1.5), 6.85 (m, 1), 7.28 (d, 2, J=8.4), 7.45 (d, 2, J=8.4); MS (APCI+) m/z 432 $(M+H)^+$.

Example 152

propyl 4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl(methyl)carbamate

The title compound was isolated as a light yellow oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 0.90 (t, 3, J= 7.3), 1.61 (m, 2), 1.90-2.01 (m, 4), 2.96 (s, 3), 3.28 (s, 3), 3.74-3.86 (m, 4), 4.05 (t, 2, J=6.5), 5.11 (s, 2), 6.70 (dt, 1, J=10.5, 2.3), 6.74 (ddd, 1, J=10.1, 2.3, 1.5), 6.85 (m, 1), 7.29 (d, 2, J=8.6), 7.46 (d, 2, J=8.6).

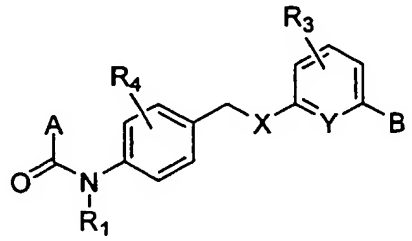
Example 153

tert-butyl 4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl(methyl)carbamate

The title compound was prepared according to the procedures described in Example 30. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9), 1.88-2.03 (m, 4), 2.91 (s, 3), 3.27 (s, 3), 3.80-3.85 (m, 4), 5.02 (s, 2), 6.61 (d, 1, J=10), 6.72 (d, 1, J=10), 6.81 (s, 1), 7.27 (app d, 2), 7.39 (d, 2, J=8.5 Hz); MS (APCI+) m/z 446 $(M+H)^+$.

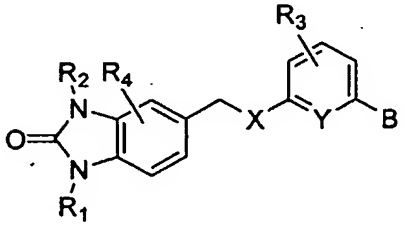
WE CLAIM:

1. A method of inhibiting interleukin 5 gene expression in a mammal comprising administering to a mammal in need of such treatment a pharmaceutically effective amount of a compound selected from the group of those falling within formula I



I

and formula II



II,

or mixtures thereof as well as their pharmaceutically acceptable salts wherein, in formulas I and II,

$R_1$ is selected from the group consisting of hydrogen and lower alkyl;

$R_2$ is selected from the group consisting of hydrogen and lower alkyl;

$R_3$ is selected from the group consisting of hydrogen, alkoxy, alkyl, cyano, halogen, haloalkoxy, haloalkyl, and $-NR_5R_6$ wherein $R_5$ and $R_6$ are independently selected from the group consisting of hydrogen and alkyl;

$R_4$ is selected from the group consisting of hydrogen, alkoxy, alkyl, cyano, halogen, haloalkoxy, haloalkyl, and $-NR_5R_6$;

A is selected from the group consisting of alkenyl, alkyl, alkynyl, alkoxy, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocyclealkyl, and $NR_7R_8$ wherein $R_7$ and $R_8$ are independently selected from the group consisting of alkenyl, alkoxyalkoxyalkyl, alkoxyalkyl, alkyl, alkynyl, aryl, arylalkyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocycle, heterocyclealkyl, hydroxyalkoxyalkyl, and hydroxyalkyl;

B is selected from the group consisting of cyclohexyl, heterocycle and $NR_9R_{10}$ wherein $R_9$ and $R_{10}$ are independently selected from the group consisting of alkenyl, alkoxyalkyl, alkyl, alkynyl, aryl, arylalkyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocycle, and heterocyclealkyl;

X is selected from the group consisting of $CH_2$ and O; and

Y is selected from the group consisting of CH and N.

2. The method according to claim 1 wherein the compound is selected from the group of those falling within formula I and

$R_1$ is lower alkyl;

$R_3$ is selected from the group consisting of hydrogen and halogen;

$R_4$ is selected from the group consisting of hydrogen and halogen;

A is heterocycle;

B is heterocycle;

X is selected from the group consisting of $CH_2$ and O; and

Y is selected from the group consisting of CH and N.

3. The method according to claim 1 wherein the compound is selected from the group of those falling within formula I and

$R_1$ is methyl;

$R_3$ is selected from the group consisting of hydrogen and fluorine;

$R_4$ is selected from the group consisting of hydrogen and chlorine;

A is selected from the group consisting of azepanyl, azetidinyl, azocanyl, furyl, piperdinyl, pyrrolyl, pyrrolidinyl, 2,5-dihydro-1H-pyrrolyl, tetrahydropyridyl, thiazolidinyl, and thiomorpholinyl;

B is selected from the group consisting of morpholinyl, piperazinyl, piperdinyl, pyrrolidinyl, tetrahydro-2H-pyranyl, and thiomorpholinyl;

X is selected from the group consisting of $CH_2$ and O; and

Y is selected from the group consisting of CH and N.

4. The method according to claim 3 wherein the compound is selected from the group consisting of

ethyl 4-{3-fluoro-5-[(4-{methyl[(2-methyl-1-pyrrolidinyl)carbonyl]amino}benzyl)oxy]phenyl}-1-piperazinecarboxylate,

N-(4-{[3-(2,6-dimethyl-4-morpholinyl)-5-fluorophenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-thiomorpholinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-hydroxy-1-piperidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-(4-acetyl-1-piperazinyl)-5-fluorophenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(1-piperidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-[4-({3-fluoro-5-[4-(2-hydroxyethyl)-1-piperazinyl]phenoxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methyl-1-piperidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(1-pyrrolidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-5-fluorophenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-hydroxy-4-phenyl-1-piperidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(3-hydroxy-1-pyrrolidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-[4-({3-fluoro-5-[4-(2-methoxyethyl)-1-piperazinyl]phenoxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1-azocanecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-3-hydroxy-N-methyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2,5-trimethyl-1-pyrrolidinecarboxamide,

(3R)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-3-hydroxy-N-methyl-1-pyrrolidinecarboxamide,

3-ethyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2,4-trimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2,5-trimethyl-2,5-dihydro-1H-pyrrole-1-carboxamide,

N-(4-{2-[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenyl]ethyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1H-pyrrole-1-carboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-2,5-dihydro-1H-pyrrole-1-carboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-3-(hydroxymethyl)-N-methyl-1-piperidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1,3-thiazolidine-3-carboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-4-(hydroxymethyl)-N-methyl-1-piperidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-3-hydroxy-N-methyl-1-piperidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-4-hydroxy-N-methyl-1-piperidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-4-thiomorpholinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-piperidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1-piperidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-3,6-dihydro-1(2H)-pyridinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1-azepanecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-4-(2-hydroxyethyl)-N-methyl-1-piperidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1-azetidinecarboxamide,

(2R)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-2-(hydroxymethyl)-N-methyl-1-pyrrolidinecarboxamide,

(2S)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-2-(hydroxymethyl)-N-methyl-1-pyrrolidinecarboxamide,

$N^1$-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-$N^1$-methyl-1,3-piperidinedicarboxamide,

N-(4-{[3-fluoro-5-(4-hydroxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-{4-[(3-fluoro-5-tetrahydro-2H-pyran-4-ylphenoxy)methyl]phenyl}-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-morpholinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

(-) N-(4-{[3-fluoro-5-(4-morpholinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

(+) N-(4-{[3-fluoro-5-(4-morpholinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(2-methyl-3-oxo-1-piperazinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

(+) N-[4-({[6-(4-hydroxytetrahydro-2H-pyran-4-yl)-2-pyridinyl]oxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide,

(-) N-[4-({[6-(4-hydroxytetrahydro-2H-pyran-4-yl)-2-pyridinyl]oxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide, and

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-2-furamide.

5. The method according to claim 1 wherein the compound is selected from those falling within formula I and

$R_1$ is lower alkyl;

$R_3$ is selected from the group consisting of hydrogen and halogen;

$R_4$ is selected from the group consisting of hydrogen and halogen;

A is $NR_7R_8$ wherein $R_7$ and $R_8$ are independently selected from the group consisting of alkenyl, alkoxyalkoxyalkyl, alkoxyalkyl, alkyl, alkynyl, aryl, arylalkyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclealkyl, hydroxyalkoxyalkyl, and hydroxyalkyl;

B is selected from the group consisting of cycloalkyl and heterocycle;

X is selected from the group cosisting of $CH_2$ and O; and

Y is selected from the group consisting of CH and N.

6. The method according to claim 1 wherein the compound is selected from those falling within formula I and

$R_1$ is methyl;

$R_3$ is selected from the group consisting of hydrogen and fluorine;

$R_4$ is selected from the group consisting of hydrogen and chlorine;

A is $NR_7R_8$ wherein $R_7$ and $R_8$ are independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkyl, alkynyl, 2-(4-hydroxyphenyl)ethyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, 2-(1,3-dioxolan-2-yl)ethyl, tetrahydro-2-furanylmethyl, hydroxyalkoxyalkyl, and hydroxyalkyl;

B is selected from the group consisting of cyclohexyl, morpholinyl, piperazinyl, piperdinyl, tetrahydo-2H-pyranyl, pyrrolidinyl, and thiomorpholinyl;

X is selected from the group consisting of $CH_2$ and O; and

Y is selected from the group consisting of CH and N.

7. The method according to claim 6 wherein the compound is selected from the group consisting of:

ethyl 4-[3-({4-[[(diethylamino)carbonyl](methyl)amino]benzyl}oxy)-5-fluorophenyl]-1-piperazinecarboxylate,

N-(4-{[3-(2,6-dimethyl-4-morpholinyl)-5-fluorophenoxy]methyl}phenyl)-N',N'-diethyl-N-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(4-thiomorpholinyl)phenoxy]methyl}phenyl)-N'-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(4-hydroxy-1-piperidinyl)phenoxy]methyl}phenyl)-N'-methylurea,

N-(4-{[3-(4-acetyl-1-piperazinyl)-5-fluorophenoxy]methyl}phenyl)-N',N'-diethyl-N-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(1-piperidinyl)phenoxy]methyl}phenyl)-N'-methylurea,

N,N-diethyl-N'-[4-({3-fluoro-5-[4-(2-hydroxyethyl)-1-piperazinyl]phenoxy}methyl)phenyl]-N'-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(4-methyl-1-piperidinyl)phenoxy]methyl}phenyl)-N'-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(1-pyrrolidinyl)phenoxy]methyl}phenyl)-N'-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(2-methyl-3-oxo-1-piperazinyl)phenoxy]methyl}phenyl)-N'-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N',N'-trimethylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethyl-N'-propylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethylurea,

N-allyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-hydroxyethyl)-N,N'-dimethylurea,

N-(3-chloro-4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N',N'-trimethylurea,

N-(cyclopropylmethyl)-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methyl-N-propylurea,

N-ethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-isopropyl-N'-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethyl-N'-(2-propynyl)urea,

N-(2-cyanoethyl)-N-cyclopropyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea,

N-allyl-N-ethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-methoxyethyl)-N,N'-dimethylurea,

N-ethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-(2-hydroxyethyl)-N'-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-isopentyl-N,N'-dimethylurea,

N-[2-(1,3-dioxolan-2-yl)ethyl]-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethylurea,

N-ethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethylurea,

N,N-diallyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N',N'-dipropylurea,

N-butyl-N-ethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea,

N-ethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methyl-N-propylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-isopropyl-N,N'-dimethylurea,

N'-cyclobutyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-(tetrahydro-2-furanylmethyl)urea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-methoxyethyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-propylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-hydroxy-1-methylethyl)-N-methylurea,

N'-(1-ethylpropyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-(2,2,2-trifluoroethyl)urea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-neopentylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-isobutyl-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-(2-methylbutyl)urea,

N'-(2-ethylhexyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-(2-propynyl)urea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-hydroxybutyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(3-hydroxy-2,2-dimethylpropyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-[2-(2-hydroxyethoxy)ethyl]-N-methylurea,

N'-allyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-methoxy-1-methylethyl)-N-methylurea,

N'-(cyanomethyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N'-cyclopropyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-isopropyl-N-methyl-N'-propylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-[(1R)-1-(hydroxymethyl)propyl]-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-(2-methyl-2-propenyl)urea,

N'-(2-fluoroethyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N'-ethyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-hydroxypropyl)-N-methylurea,

N'-(cyclopropylmethyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N'-(2-ethylbutyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N'-cyclopentyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N'-(1,2-dimethylpropyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N'-sec-butyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N'-[bicyclo[2.2.1]hept-2-yl]-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-[2-(4-hydroxyphenyl)ethyl]-N-methylurea,

N'-(2-cyanoethyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-hydroxyethyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-[1-(hydroxymethyl)cyclopentyl]-N-methylurea,

N'-(2,2-dimethylcyclopentyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-isopropyl-N-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea,

N-ethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-(2-methoxyethyl)-N'-methylurea,

N-butyl-N-(cyanomethyl)-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea,

N-butyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-isopropyl-N'-(2-methoxyethyl)-N-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(4-hydroxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea,

N-(4-{[3-fluoro-5-(4-hydroxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N',N'-trimethylurea,

N-[4-({3-fluoro-5-[4-(2-propynyloxy)tetrahydro-2H-pyran-4-yl]phenoxy}methyl)phenyl]-N,N',N'-trimethylurea,

N,N-diethyl-N'-(4-{[3-(4-ethyltetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea,

ethyl 4-[3-({4-[[(diethylamino)carbonyl](methyl)amino]benzyl}oxy)phenyl]tetrahydro-2H-pyran-4-carboxylate,

N,N-diethyl-N'-(4-{[3-fluoro-5-(1-hydroxycyclohexyl)phenoxy]methyl}phenyl)-N'-methylurea,

N,N-diethyl-N'-{4-[(3-fluoro-5-tetrahydro-2H-pyran-4-ylphenoxy)methyl]phenyl}-N'-methylurea,

tert-butyl 4-[3-({4-[[(diethylamino)carbonyl](methyl)amino]benzyl}oxy)-5-fluorophenyl]-4-hydroxy-1-piperidinecarboxylate,

N-allyl-N'-(4-{[3-(trans-1,4-dimethoxycyclohexyl)-5-fluorophenoxy]methyl}phenyl)-N,N'-dimethylurea,

N-(4-{[3-(trans-1,4-dimethoxycyclohexyl)-5-fluorophenoxy]methyl}phenyl)-N',N'-diethyl-N-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(4-morpholinyl)phenoxy]methyl}phenyl)-N'-methylurea, and

N,N-diethyl-N'-[4-({[6-(4-hydroxytetrahydro-2H-pyran-4-yl)-2-pyridinyl]oxy}methyl)phenyl]-N'-methylurea.

8. The method according to claim 1 wherein the compound is selected from those falling within formula I and

$R_1$ is lower alkyl;

$R_3$ is selected from the group consisting of hydrogen and halogen;

$R_4$ is selected from the group consisting of hydrogen and halogen;

A is heterocycle;

B is $NR_9R_{10}$ wherein $R_9$ and $R_{10}$ are independently selected from the group consisting of alkenyl, alkoxyalkyl, alkyl, alkynyl, aryl, arylalkyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocycle, and heterocyclealkyl;

X is selected from the group consisting of $CH_2$ and O; and

Y is selected from the group consisting of CH and N.

9. The method according to claim 1 wherein the compound is selected from those falling within formula I and

$R_1$ is methyl;

$R_3$ is selected from the group consisting of hydrogen and fluorine;

$R_4$ is selected from the group consisting of hydrogen and chlorine;

A is pyrrolidinyl;

B is $NR_9R_{10}$ wherein $R_9$ and $R_{10}$ are independently selected from the group consisting of hydrogen, alkoxyalkyl, and alkyl;

X is selected from the group consisting of $CH_2$ and O; and

Y is selected from the group consisting of CH and N.

10. The method according to claim 9 wherein the compound is selected from the group consisting of

N-[4-({3-[bis(2-methoxyethyl)amino]-5-fluorophenoxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide and

N-[4-({3-[ethyl(2-methoxyethyl)amino]-5-fluorophenoxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide.

11. The method according to claim 1 wherein the compound is selected from those falling within formula I and

$R_1$ is lower alkyl;

$R_3$ is selected from the group consisting of hydrogen and halogen;

$R_4$ is selected from the group consisting of hydrogen and halogen;

A is $NR_7R_8$ wherein $R_7$ and $R_8$ are independently selected from hydrogen, alkenyl, alkoxyalkoxyalkyl, alkoxyalkyl, alkyl, alkynyl, aryl, arylalkyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclealkyl, hydroxyalkoxyalkyl, and hydroxyalkyl;

B is $NR_9R_{10}$ wherein $R_9$ and $R_{10}$ are independently selected from alkenyl, alkoxyalkyl, alkyl, alkynyl, aryl, arylalkyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocycle, and heterocyclealkyl;

X is selected from the group consisting of $CH_2$ and O; and

Y is selected from the group consisting of CH and N.

12. The method according to claim 1 wherein the compound is selected from those falling within formula I and

$R_1$ is methyl;

$R_3$ is selected from the group consisting of hydrogen and fluorine;

$R_4$ is selected from the group consisting of hydrogen and chlorine;

A is $NR_7R_8$ wherein $R_7$ and $R_8$ are independently selected from the group consisting of hydrogen and alkyl;

B is $NR_9R_{10}$ wherein $R_9$ and $R_{10}$ are independently selected from the group consisting of hydrogen, alkoxyalkyl, alkyl, and cycloalkyl;

X is selected from the group consisting of $CH_2$ and O; and

Y is selected from the group consisting of CH and N.

13. The method according to claim 12 wherein the compound is selected from the group consisting of

N-[4-({3-[bis(2-methoxyethyl)amino]-5-fluorophenoxy}methyl)phenyl]-N',N'-diethyl-N-methylurea,

N-(4-{[3-(cyclopentylamino)-5-fluorophenoxy]methyl}phenyl)-N',N'-diethyl-N-methylurea,

N-(4-{[3-(cyclohexylamino)-5-fluorophenoxy]methyl}phenyl)-N',N'-diethyl-N-methylurea, and

N,N-diethyl-N'-[4-({3-[ethyl(2-methoxyethyl)amino]-5-fluorophenoxy}methyl)phenyl]-N'-methylurea.

14. The method according to claim 1 wherein the compound is selected from the group falling within formula I and

$R_1$ is lower alkyl;

$R_3$ is selected from the group consisting of hydrogen and halogen;

$R_4$ is selected from the group consisting of hydrogen and halogen;

A is selected from the group consisting of alkoxy, alkyl, and cycloalkyl;

B is heterocycle;

X is selected from the group consisting of $CH_2$ and O; and

Y is selected from the group consisting of CH and N.

15. The method according to claim 1 wherein the compound is selected from the group of those falling within formula I and

$R_1$ is methyl;

$R_3$ is selected from the group consisting of hydrogen and fluorine;

$R_4$ is selected from the group consisting of hydrogen and chlorine;

A is selected from the group consisting of alkoxy, alkyl, and cycloalkyl;

B is tetrahydro-2H-pyranyl;

X is selected from the group consisting of $CH_2$ and O; and

Y is selected from the group consisting of CH and N.

16. The method according to claim 15 wherein the compound is selected from the group consisting of

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,3,3-trimethylbutanamide,

2-ethyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylbutanamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2,2-trimethylpropanamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylcyclopentanecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylcyclopropanecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2-dimethylpropanamide,

isopropyl 4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl(methyl)carbamate,

propyl 4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl(methyl)carbamate, and

tert-butyl 4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl(methyl)carbamate.

17. The method according to claim 1 wherein the compound is selected from those falling within formula II and

$R_1$ is lower alkyl;

$R_2$ is lower alkyl;

$R_3$ is selected from the group consisting of hydrogen and halogen;

$R_4$ is selected from the group consisting of hydrogen and halogen;

B is selected from the group consisting of cycloalkyl and heterocycle;

X is selected from the group consisting of $CH_2$ and O; and

Y is selected from the group consisting of CH and N.

18. The method according to claim 1 wherein the compound is selected from those falling within formula II and

$R_1$ is methyl;

$R_2$ is methyl;

$R_3$ is selected from the group consisting of hydrogen and fluorine;

$R_4$ is selected from the group consisting of hydrogen and chlorine;

B is selected from the group consisting of cyclohexyl, piperdinyl, and tetrahydro-2H-pyranyl;

X is selected from the group consisting of $CH_2$ and O; and

Y is selected from the group consisting of CH and N.

19. The method according to claim 18 wherein the compound is selected from the gorup consisting of

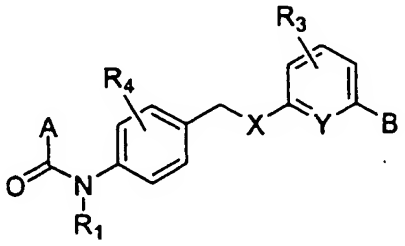
5-{[3-(1-benzyl-4-hydroxy-4-piperidinyl)-5-fluorophenoxy]methyl}-1,3-dimethyl-1,3-dihydro-2H-benzimidazol-2-one,

5-{[3-(trans-1,4-dimethoxycyclohexyl)-5-fluorophenoxy]methyl}-1,3-dimethyl-1,3-dihydro-2H-benzimidazol-2-one,

5-{[3-fluoro-5-(8-hydroxy-1,4-dioxaspiro[4.5]dec-8-yl)phenoxy]methyl}-1,3-dimethyl-1,3-dihydro-2H-benzimidazol-2-one, and

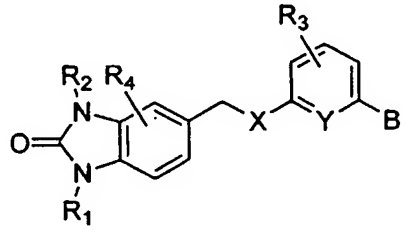
5-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}-1,3-dimethyl-1,3-dihydro-2H-benzimidazol-2-one.

20. A pharmaceutical composition comprising a therapeutically effective amount of one or more compounds selected from the group of those falling within formula I



I,

and formula II,



II,

or mixtures thereof as well as their pharmaceutically acceptable salts in combination with a pharmaceutically acceptable carrier wherein, in formulas I and II,

$R_1$ is selected from the group consisting of hydrogen and lower alkyl;

$R_2$ is selected from the group consisting of hydrogen and lower alkyl;

$R_3$ is selected from the group consisting of hydrogen, alkoxy, alkyl, cyano, halogen, haloalkoxy, haloalkyl, and $-NR_5R_6$ wherein $R_5$ and $R_6$ are independently selected from the group consisting of hydrogen and alkyl;

$R_4$ is selected from the group consisting of hydrogen, alkoxy, alkyl, cyano, halogen, haloalkoxy, haloalkyl, and $-NR_5R_6$;

A is selected from the group consisting of alkenyl, alkyl, alkynyl, alkoxy, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocyclealkyl, and $NR_7R_8$ wherein $R_7$ and $R_8$ are independently selected from the group consisting of alkenyl, alkoxyalkoxyalkyl, alkoxyalkyl, alkyl, alkynyl, aryl, arylalkyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocycle, heterocyclealkyl, hydroxyalkoxyalkyl, and hydroxyalkyl;

B is selected from the group consisting of cyclohexyl, heterocycle and $NR_9R_{10}$ wherein $R_9$ and $R_{10}$ are independently selected from the group consisting of alkenyl, alkoxyalkyl, alkyl, alkynyl, aryl, arylalkyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocycle, and heterocyclealkyl;

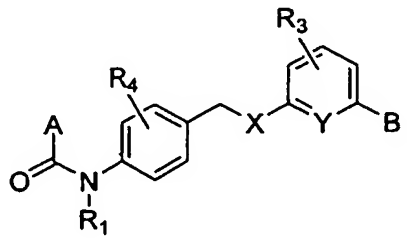
X is selected from the group consisting of $CH_2$ and O; and

Y is selected from the group consisting of CH and N.

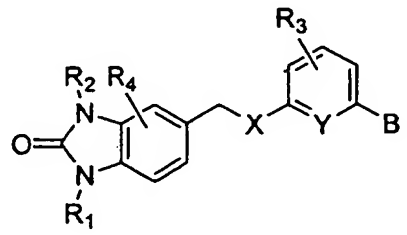
21. A method of treating an allergic disease in a mammal comprising administering to a mammal in need of such treatment, a pharmaceutically effective amount of the pharmaceutical composition of claim 20.

22. The method according to claim 21 wherein the allergic disease is asthma.

23. A compound selected from the group of compounds consisting of those represented by formula I and formula II below



I



II,

or their pharmaceutically acceptable salts, wherein, in formulas I and II,

$R_1$ is selected from the group consisting of hydrogen and lower alkyl;

$R_2$ is selected from the group consisting of hydrogen and lower alkyl;

$R_3$ is selected from the group consisting of hydrogen, alkoxy, alkyl, cyano, halogen, haloalkoxy, haloalkyl, and $-NR_5R_6$ wherein $R_5$ and $R_6$ are independently selected from the group consisting of hydrogen and alkyl;

$R_4$ is selected from the group consisting of hydrogen, alkoxy, alkyl, cyano, halogen, haloalkoxy, haloalkyl, and $-NR_5R_6$;

A is selected from the group consisting of alkenyl, alkyl, alkynyl, alkoxy, aryl, arylalkyl, cycloalkyl,cycloalkylalkyl, heterocycle, heterocyclealkyl, and $NR_7R_8$ wherein $R_7$ and $R_8$ are independently selected from the group consisting of alkenyl, alkoxyalkoxyalkyl, alkoxyalkyl, alkyl, alkynyl, aryl, arylalkyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocycle, heterocyclealkyl, hydroxyalkoxyalkyl, and hydroxyalkyl;

B is selected from the group consisting of heterocycle and $NR_9R_{10}$ wherein $R_9$ and $R_{10}$ are independently selected from the group consisting of alkenyl, alkoxyalkyl, alkyl, alkynyl, aryl, arylalkyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocycle, and heterocyclealkyl;

X is selected from the group consisting of $CH_2$ and O; and

Y is selected from the group consisting of CH and N;

with the proviso that for compounds of formula I when $R_4$ is hydrogen and A is piperdinyl, morpholinyl, thiomorpholinyl, piperazinyl, or $NR_7R_8$ and $R_7$ and $R_8$ are independently selected from the group consisting of hydrogen, alkyl, haloalkyl, and hydroxyalkyl then B is other than tetrahydro-2H-pyran-4-yl optionally substituted with 1

subsituent selected from the group consisting of hydroxy and alkoxy or cyclohexyl optionally substituted with 1 subsituent selected from the group consisting of hydroxy and alkoxy; and

with the further proviso that for compounds of formula II when $R_3$ is hydrogen and $R_4$ is hydrogen then B is other than cyclohexyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkyl, and hydroxy.

24. A compound according to claim 23 of formula I wherein

$R_1$ is selected from the group consisting of hydrogen and lower alkyl;

$R_3$ is selected from the group consisting of hydrogen and halogen;

$R_4$ is selected from the group consisting of hydrogen and halogen;

A is selected from the group consisting of alkyl, alkoxy, cycloalkyl, heterocycle, and $NR_7R_8$ wherein $R_7$ and $R_8$ are independently selected from the group consisting of alkenyl, alkoxyalkyl, alkyl, alkynyl, arylalkyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclealkyl, hydroxyalkoxyalkyl, and hydroxyalkyl;

B is selected from the group consisting of heterocycle and $NR_9R_{10}$ wherein $R_9$ and $R_{10}$ are independently selected from alkoxyalkyl, alkyl, and cycloalkyl;

X is selected from the group consisting of $CH_2$ and O; and

Y is selected from the group consisting of CH and N.

25. A compound according to claim 23 of formula I wherein

$R_1$ is methyl;

$R_3$ is selected from the group consisting of hydrogen and fluorine;

$R_4$ is selected from the group consisting of hydrogen and chlorine;

A is selected from the group consisting of azetidinyl, azepanyl, azocanyl, furyl, pyrrolyl, pyrrolidinyl, pyrrolinyl, thiazolidinyl, and tetrahydropyridyl;

B is selected from the group consisting of morpholinyl, piperazinyl, piperdinyl, tetrahydro-2H-pyranyl, pyrrolidinyl, thiomorpholinyl, and $NR_9R_{10}$ wherein $R_9$ and $R_{10}$ are independently selected from the group consisting of alkoxyalkyl and alkyl;

X is selected from the group consisting of $CH_2$ and O; and

Y is CH.

26. A compound according to claim 25 selected from the group consisting of ethyl 4-{3-fluoro-5-[(4-{methyl[(2-methyl-1-pyrrolidinyl)carbonyl]amino}benzyl)oxy]phenyl}-1-piperazinecarboxylate,

N-[4-({3-[bis(2-methoxyethyl)amino]-5-fluorophenoxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-(2,6-dimethyl-4-morpholinyl)-5-fluorophenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-thiomorpholinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-hydroxy-1-piperidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-(4-acetyl-1-piperazinyl)-5-fluorophenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(1-piperidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-[4-({3-fluoro-5-[4-(2-hydroxyethyl)-1-piperazinyl]phenoxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methyl-1-piperidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-[4-({3-[ethyl(2-methoxyethyl)amino]-5-fluorophenoxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(1-pyrrolidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-5-fluorophenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-hydroxy-4-phenyl-1-piperidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(3-hydroxy-1-pyrrolidinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-[4-({3-fluoro-5-[4-(2-methoxyethyl)-1-piperazinyl]phenoxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1-azocanecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-3-hydroxy-N-methyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2,5-trimethyl-1-pyrrolidinecarboxamide,

(3R)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-3-hydroxy-N-methyl-1-pyrrolidinecarboxamide,

3-ethyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2,4-trimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2,5-trimethyl-2,5-dihydro-1H-pyrrole-1-carboxamide,

N-(4-{2-[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenyl]ethyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1H-pyrrole-1-carboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-2,5-dihydro-1H-pyrrole-1-carboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1,3-thiazolidine-3-carboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-3,6-dihydro-1(2H)-pyridinecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1-azepanecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-1-azetidinecarboxamide,

(2R)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-2-(hydroxymethyl)-N-methyl-1-pyrrolidinecarboxamide,

(2S)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-2-(hydroxymethyl)-N-methyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-hydroxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-{4-[(3-fluoro-5-tetrahydro-2H-pyran-4-ylphenoxy)methyl]phenyl}-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(4-morpholinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

(-) N-(4-{[3-fluoro-5-(4-morpholinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

(+) N-(4-{[3-fluoro-5-(4-morpholinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide,

N-(4-{[3-fluoro-5-(2-methyl-3-oxo-1-piperazinyl)phenoxy]methyl}phenyl)-N,2-dimethyl-1-pyrrolidinecarboxamide, and

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-2-furamide.

27. A compound according to claim 23 of formula I wherein

$R_1$ is methyl;

$R_3$ is selected from the group consisting of hydrogen and fluorine;

$R_4$ is selected from the group consisting of hydrogen and chlorine;

A is $NR_7R_8$ wherein $R_7$ and $R_8$ are independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkyl, alkynyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, 2-(1,3-dioxolan-2-yl)ethyl, tetrahydro-2-furanylmethyl, hydroxyalkoxyalkyl, and 2-phenylethyl;

B is selected from the group consisting of tetrahydro-2H-pyranyl and cyclohexyl;

X is selected from the group consisting of $CH_2$ and O; and

Y is CH.

28. A compound according to claim 27 selected from the group consisting of

N-allyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethylurea,

N-(3-chloro-4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N',N'-trimethylurea,

N-(cyclopropylmethyl)-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methyl-N-propylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethyl-N'-(2-propynyl)urea,

N-(2-cyanoethyl)-N-cyclopropyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea,

N-allyl-N-ethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-methoxyethyl)-N,N'-dimethylurea,

N-[2-(1,3-dioxolan-2-yl)ethyl]-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N'-dimethylurea,

N,N-diallyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea,

N'-cyclobutyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-(tetrahydro-2-furanylmethyl)urea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-methoxyethyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-(2-propynyl)urea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-[2-(2-hydroxyethoxy)ethyl]-N-methylurea,

N'-allyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-(2-methoxy-1-methylethyl)-N-methylurea,

N'-(cyanomethyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N'-cyclopropyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methyl-N'-(2-methyl-2-propenyl)urea,

N'-(cyclopropylmethyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N'-cyclopentyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N'-[bicyclo[2.2.1]hept-2-yl]-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-[2-(4-hydroxyphenyl)ethyl]-N-methylurea,

N'-(2-cyanoethyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-[1-(hydroxymethyl)cyclopentyl]-N-methylurea,

N'-(2,2-dimethylcyclopentyl)-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylurea,

N-ethyl-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-(2-methoxyethyl)-N'-methylurea,

N-butyl-N-(cyanomethyl)-N'-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea,

N-[4-({3-fluoro-5-[4-(2-propynyloxy)tetrahydro-2H-pyran-4-yl]phenoxy}methyl)phenyl]-N,N',N'-trimethylurea,

N,N-diethyl-N'-(4-{[3-(4-ethyltetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N'-methylurea,

ethyl 4-[3-({4-[[(diethylamino)carbonyl](methyl)amino]benzyl}oxy)phenyl]tetrahydro-2H-pyran-4-carboxylate, and

N,N-diethyl-N'-{4-[(3-fluoro-5-tetrahydro-2H-pyran-4-ylphenoxy)methyl]phenyl}-N'-methylurea.

29. A compound according to claim 23 of formula I wherein

$R_1$ is methyl;

$R_3$ is selected from the group consisting of hydrogen and fluorine;

$R_4$ is selected from the group consisting of hydrogen and chlorine;

A is $NR_7R_8$ wherein $R_7$ and $R_8$ are independently selected from the group consisting of hydrogen and alkyl;

B is selected from the group consisting of morpholinyl, piperazinyl, piperdinyl, pyrrolidinyl, thiomorpholinyl, and $NR_9R_{10}$ wherein $R_9$ and $R_{10}$ are independently selected from the group consisting of hydrogen, alkoxyalkyl, alkyl, and cycloalkyl;

X is selected from the group consisting of $CH_2$ and O; and

Y is CH.

30. A compound according to claim 29 selected from the group consisting of ethyl 4-[3-({4-[[(diethylamino)carbonyl](methyl)amino]benzyl}oxy)-5-fluorophenyl]-1-piperazinecarboxylate,

N-[4-({3-[bis(2-methoxyethyl)amino]-5-fluorophenoxy}methyl)phenyl]-N',N'-diethyl-N-methylurea,

N-(4-{[3-(2,6-dimethyl-4-morpholinyl)-5-fluorophenoxy]methyl}phenyl)-N',N'-diethyl-N-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(4-thiomorpholinyl)phenoxy]methyl}phenyl)-N'-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(4-hydroxy-1-piperidinyl)phenoxy]methyl}phenyl)-N'-methylurea,

N-(4-{[3-(4-acetyl-1-piperazinyl)-5-fluorophenoxy]methyl}phenyl)-N',N'-diethyl-N-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(1-piperidinyl)phenoxy]methyl}phenyl)-N'-methylurea,

N-(4-{[3-(cyclopentylamino)-5-fluorophenoxy]methyl}phenyl)-N',N'-diethyl-N-methylurea,

N-(4-{[3-(cyclohexylamino)-5-fluorophenoxy]methyl}phenyl)-N',N'-diethyl-N-methylurea,

N,N-diethyl-N'-[4-({3-fluoro-5-[4-(2-hydroxyethyl)-1-piperazinyl]phenoxy}methyl)phenyl]-N'-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(4-methyl-1-piperidinyl)phenoxy]methyl}phenyl)-N'-methylurea,

N,N-diethyl-N'-[4-({3-[ethyl(2-methoxyethyl)amino]-5-fluorophenoxy}methyl)phenyl]-N'-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(1-pyrrolidinyl)phenoxy]methyl}phenyl)-N'-methylurea,

N,N-diethyl-N'-(4-{[3-fluoro-5-(2-methyl-3-oxo-1-piperazinyl)phenoxy]methyl}phenyl)-N'-methylurea,

tert-butyl 4-[3-({4-[[(diethylamino)carbonyl](methyl)amino]benzyl}oxy)-5-fluorophenyl]-4-hydroxy-1-piperidinecarboxylate, and

N,N-diethyl-N'-(4-{[3-fluoro-5-(4-morpholinyl)phenoxy]methyl}phenyl)-N'-methylurea.

31. A compound according to claim 23 of formula I wherein

$R_4$ is halogen.

32. A compound according to claim 23 of formula I wherein

$R_4$ is chlorine.

33. A compound according to claim 23 of formula I wherein

$R_1$ is methyl;

$R_3$ is selected from the group consisting of hydrogen and fluorine;

$R_4$ is chlorine;

A is $NR_7R_8$ wherein $R_7$ and $R_8$ are independently selected from the group consisting of hydrogen and alkyl;

B is tetrahydro-2H-pyranyl;

X is O; and

Y is CH.

34. A compound according to claim 33 that is N-(3-chloro-4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,N',N'-trimethylurea.

35. A compound according to claim 23 of formula I wherein

Y is N.

36. A compound according to claim 23 of formula I wherein

$R_1$ is methyl;

$R_3$ is hydrogen;

$R_4$ is hydrogen;

A is selected from the group consisting of pyrrolidinyl and $NR_7R_8$ wherein $R_7$ and $R_8$ are independently selected from the group consisting of hydrogen and alkyl;

B is tetrahydro-2H-pyranyl;

X is O; and

Y is N.

37. A compound according to claim 36 selected from the group consisting of

(+) N-[4-({[6-(4-hydroxytetrahydro-2H-pyran-4-yl)-2-pyridinyl]oxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide,

(-) N-[4-({[6-(4-hydroxytetrahydro-2H-pyran-4-yl)-2-pyridinyl]oxy}methyl)phenyl]-N,2-dimethyl-1-pyrrolidinecarboxamide, and

N,N-diethyl-N'-[4-({[6-(4-hydroxytetrahydro-2H-pyran-4-yl)-2-pyridinyl]oxy}methyl)phenyl]-N'-methylurea.

38. A compound according to claim 23 of formula I wherein

$R_1$ is selected from the group consisting of hydrogen and alkyl;

$R_3$ is selected from the group consisting of hydrogen and halogen;

$R_4$ is selected from the group consisting of hydrogen and halogen;

A is selected from the group consisting of alkoxy, alkyl, and cycloalkyl;

X is O; and

Y is CH.

39. A compound according to claim 23 of formula I wherein

$R_1$ is methyl;

$R_3$ is fluorine;

$R_4$ is hydrogen;

A is selected from the group consisting of alkoxy, alkyl, and cycloalkyl;

B is tetrahydro-2H-pyranyl;

X is O; and

Y is CH.

40. A compound according to claim 39 selected from the group consisting of

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,3,3-trimethylbutanamide,

2-ethyl-N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylbutanamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2,2-trimethylpropanamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylcyclopentanecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N-methylcyclopropanecarboxamide,

N-(4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl)-N,2-dimethylpropanamide,

isopropyl 4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl(methyl)carbamate,

propyl 4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl(methyl)carbamate, and

tert-butyl 4-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}phenyl(methyl)carbamate.

41. A compound according to claim 23 of formula II wherein

$R_1$ is methyl;

$R_2$ is methyl;

$R_3$ is halogen;

$R_4$ is selected from the group consisting of hydrogen and halogen;

X is selected from the group consisting of $CH_2$ and O; and

Y is selected from the group consisting of CH and N.

42. A compound according to claim 23 of formula II wherein

$R_1$ is methyl;

$R_2$ is methyl;

$R_3$ is fluorine;

$R_4$ is hydrogen;

B is selected from the group consisting of cyclohexyl, piperdinyl, and tetrahydro-2H-pyranyl;

X is O; and

Y is CH.

43. A compound according to claim 42 selected from the group consisting of

5-{[3-(1-benzyl-4-hydroxy-4-piperidinyl)-5-fluorophenoxy]methyl}-1,3-dimethyl-1,3-dihydro-2H-benzimidazol-2-one,

5-{[3-(trans-1,4-dimethoxycyclohexyl)-5-fluorophenoxy]methyl}-1,3-dimethyl-1,3-dihydro-2H-benzimidazol-2-one,

5-{[3-fluoro-5-(8-hydroxy-1,4-dioxaspiro[4.5]dec-8-yl)phenoxy]methyl}-1,3-dimethyl-1,3-dihydro-2H-benzimidazol-2-one, and

5-{[3-fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy]methyl}-1,3-dimethyl-1,3-dihydro-2H-benzimidazol-2-one.

44. A method for treating asthma in a mammal which comprises administering to a mammal in need of such treatment, a pharmaceutically effective amount of a selective interleukin 5 gene expression inhibitor.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/34229

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D309/04 C07D295/20 C07D309/12 C07D405/12 C07D417/12
C07C275/32 C07D207/12 C07D295/08 C07D241/08 C07D405/04
C07D235/26 A61K31/35 A61K31/40 A61K31/41 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | G.C. CRAWLEY ET. AL.: "Methoxytetrahydropyrans. A New Series of Selective and Orally Potent 5-Lipoxygenase Inhibitors" JOURNAL OF MEDICINAL CHEMISTRY, vol. 35, no. 14, 10 July 1996 (1996-07-10), pages 2600-9, XP002164408 Table IV, compound 4gg, table V, compound 4pp | 21,23, 40-42 |
| A | US 5 622 977 A (WARRELOW ET. AL.) 22 April 1997 (1997-04-22) claims; examples | 1-44 |
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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 30 March 2001 | 20.04.2001 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2 | |

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# INTERNATIONAL SEARCH REPORT

International Application N
PCT/US 00/34

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/44 A61K31/495 A61P11/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| | | |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 30 March 2001 | 20.04.2001 |
| Name and mailing address of the ISA<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk | Authorized officer |

# INTERNATIONAL SEARCH REPORT

ational application No.
PCT/US 00/34229

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-20 , 22 and 44 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern[illegible]al Application
PCT/US 00/3[illegible]

| Patent document cited in search report | Publication date | Patent family member(s) | Pu[illegible] a[illegible] |
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